ADVERSE OUTCOMES OF FIRST-LINE INTEGRASE INHIBITOR-BASED SINGLE-TABLET ANTIRETROVIRAL REGIMENS IN THE SPANISH VACH COHORT

Ramon Teira[1], Marta Montero[2], Pepa Galindo[3], Belén de la Fuente[4], Lola Merino[5], Francisco Téllez[6], Mª Antonia Sepúlveda[7], Nuria Espinosa[8], Pepa Muñoz[9], Teresa Puig[10], Alberto Terrón[11], Vicente Estrada[12], Josefina García[13], Manuel Castaño[14], Paloma Geijo[15], Esteban Ribera[16], Elisa Martínez [17], Elisabeth Deig[18], Pere Domingo[19], Bernardino Roca[20], Agustín Muñoz-Sanz[21], Fernando Lozano[22], Mª Mar Gutiérrez[19], Joaquim Peraire[23] VACH Study Group

1 Hospital de Sierrallana,Torrelavega; 2 Hospital La Fe, Valencia; 3 Hospital Clínico, Valencia; 4 Hospital de Cabueñes, Gijón; 5 Hospital Infanta Elena, Huelva; 6 Hospital Clínico, Puerto Real; 7 Hospital Virgen de la Salud, Toledo; 8 Hospital Virgen del Rocío, Sevilla; 9 Hospital de Basurto, Bilbao; 10 Hospital Arnau de Vilanova, Lleida; 11 Hospital del SAS, Jerez de la Frontera; 12 Hospital Clínico de San Carlos, Madrid; 13 Hospital de Santa Lucía, Cartagena; 14 Hospital Carlos Haya, Málaga; 15 Hospital Virgen de la Luz, Cuenca; 16 Hospital Vall d´Hebrón,Barcelona; 17 Hospital de Albacete, Albacete; 18 Hospital General de Granollers; 19 Hospital de la Santa Creu i Sant Pau, Barcelona; 20 Hospital General, Castellón; 21 Hospital Infanta Cristina, Badajoz; 22 Hospital de Valme, Sevilla; Hospital Joan XXIII, Tarragona. All in Spain

BACKGROUND

The co-formulation of dolutegravir (DGV) with abacavir and lamivudine in a single pill under the brand name Triumeq® constitute the only complete single-tablet regimen (STR) preferred for the initiation of antiretroviral treatment (ART) in every national and international guidelines. The co-formulation of elvitegravir (EVG) with cobicistat, emtricitabine and tenofovir-alafenamide branded Genvoya® is preferred in the EACS and in the US-DHHS guidelines, and it is considered a first-line alternative in most other international and national guidelines. Both combinations have shown high levels both of efficacy and tolerability in their pivotal trials. In addition, the convenience of the STR, only shared by the otherwise less preferred co-formulations of rilpivirine and efavirenz, have favored their widespread use. However, of the 3 integrase strand transfer inhibitors (INSTI) approved by the European Medicines Agency and available for use in Spain, raltegravir, DGV and EVG , only the first 2 have been directly compared in a clinical trial, designed to demonstrate non-inferiority of DGV with respect to raltegravir. In their respective registration studies, a great efficacy has been demonstrated to suppress viral replication and render HIV viral load undetectable with all three, although there are some differences in the design and characteristics of the samples that make interpretation difficult. Anticipating the very low probability that a clinical trial will be promoted to complete the comparison scheme between these 3 drugs, we decided to study the comparative performance of DGV and EVG in an unselected cohort of HIV infected patients who initiated antiretroviral treatment with Triumeq or Genvoya.

METHODS

The VACH Cohort is an open cohort of HIV-infected adults that was established in Spain in 2000 by 16 (currently 23) hospital-based HIV clinics. Patients are included in the cohort provided that they are at least 18 years old and they give their informed consent. Our studies and the Cohort conform to Spanish laws and regulations regarding confidentiality, patient autonomy, data protection and medical investigation.

For this study we selected, from the VACH database, those patients who had started ART with either Triumeq or Genvoya. We dismissed those who had less than one year of follow-up after treatment initiation. In the remaining patients, we studied the incidence of adverse outcomes (AO) which we defined as any of the following:

- Change of ART regimen for any cause
- Treatment discontinuation
- Loss to follow-up
- Death

Time of follow-up was that counted from treatment initiation until the occurrence of an AO or administrative censoring. We constructed Kaplan-Meier curves of time to an AO for patients starting ART with Triumeq and with Genvoya and compared them by means of the log-rank test. Then we studied possible associations of other variables with AOs in simple bivariate analyses using squared-chi tests or Student´s T tests. Those variables that showed an association with the outcomes (p value less than 0.1) were included in Cox regression models with and without the inclusion of the ART regimen.

We performed a secondary analysis restricted to those patients who had at least an HIV viral load determination after 360 days of treatment initiation, in which we classified those cases who had a viral load higher than 50 copies/mL as an AO, in addition to the four AO specified above. To ascertain the relationship between predictive variables, with a special interest in the study treatments, and this new definition of AO, we used logistic regression models.

RESULTS

Out of 1233 patients who had started ART with Genvoya or Triumeq, 807 fufilled the other selection criteria. 343 received Genvoya and 464, Triumeq. There were 683 males and 124 females. Tables 1-6 show the most relevant characteristics of the studied population by treatment group and their relationship with treatment outcomes. During follow-up 130 patients experience an AO: 56 of those starting with Genvoya and 74 with Triumeq. Figure 1 shobws the Kaplan-Meier curves of time until an AO (p=.244, log-rank test). Table7 shows the results of the final Cox model of factors associated with an AO. Nadir CD4 cell count, baseline (log10) viral load (VL) and mechanism of HIV transmission were independently associated with outcomes, but not sex, age, treatment regimen or ethnicity. Tables 8 and 9 show the results of the secondary analysis with VL>50 at the end of follow-up added as to the AO definition.

Figure1. Kaplan-Meier curves of time to an AO, per study combination.

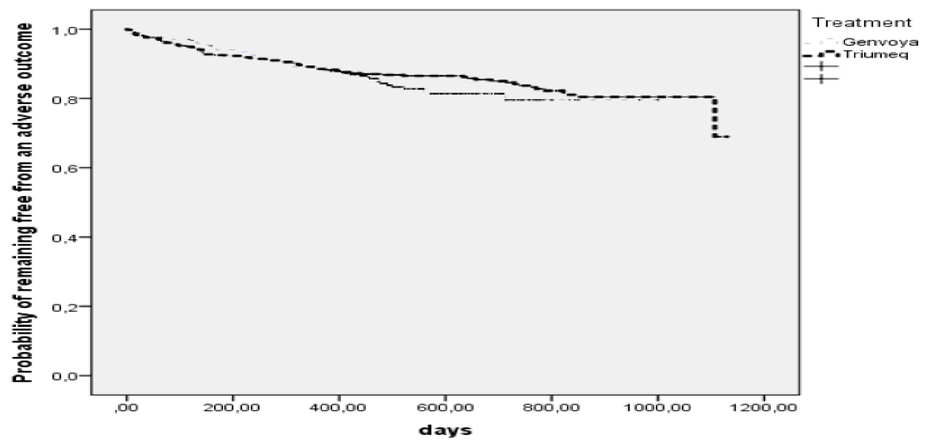

Table 1. characteristics of the population studied.

		GENVOYA	TRIUMEQ	ALL	P VALUE
AGE		35 (28-45)	36 (30-43)	36 (29-44)	0.96
NADIR CD4		369 (205-522)	405 (241-549)	394 (222-531)	0,05
LOG10VL		4.83 (4.23-5.31)	4.63 (4.13-5.17)	4.49 (4.17-5.29)	0.081
VHC	NEG.	245	344	589	0.537
	NR	71	82	153	
	POS	26	38	64	
VHB	NEG	268	364	632	0.03

Table 2. Characteristics of the population studied (2).

		GENVOYA	TRIUMEQ	ALL	P VALUE
SEX	MALE	288	394	682	0.89
	FEMALE	54	70	124	
ETHNICITY	WHITE	202	303	505	<0.005
	BLACK	18	8	26	
	HISPANIC	16	37	53	
	OTHERS	9	10	19	
	UNKNOWN				

Table 3. Adverse outcomes and predictive factors.

		AO	NO AO	ALL	P VALUE
AGE		38 (30-49)	36 (30-43)	36 (29-44)	0.015
NADIR CD4		306 (115-460)	399 (258-544)	394 (222-531)	<0.000
LOG10VL		4.92 (4.27-5.59)	4.64 (4.14-5.18)	4.49 (4.17-5.29)	0.0003
VHC	NEG.	95	494	589	0.006
	NR	18	135	153	
	POS	16	48	64	
VHB	NEG	110	522	632	0.09

Table 4. Adverse outcomes and predictive factors (2).

		AO	NO AO	ALL	P VALUE
SEX	MALE	106	576	682	0.89
	FEMALE	23	101	124	
ETHNICITY	WHITE	97	408	505	0.027
	BLACK	2	24	26	
	HISPANIC	6	47	53	
	OTHERS	1	18	19	
	UNKNOWN	23	180	203	

Table 5. Mechanism of HIV transmission, treatment-combination and outcomes.

		HSH	HTSX	IVDU	OTHER	TOTAL	P VALUE
TREATMENT	GENVOYA	190	96	18	38	342	0.113
	TRIUMEQ	295	108	24	37	464	
AO	YES	80	32	10	7	129	0.063
	NO	405	172	32	68	677	

Table 6. Outcomes per study group.

		GENVOYA	TRIUMEQ	TOTAL	P VALUE
OUTCOME	NO AO: REMAINS ON RX	276	364	640	0.959
	AO: CHANGE OF RX	50	62	112	
	AO: DIED	2	4	6	
	AO: LOST TO FU	9	22	31	
	AO: DISCONTINUED	5	12	17	

Table 7. Proportional hazards regression models of time to an AO.

		RH	95% CI	P VALUE
NADIR CD4		0.999	0.998-0.999	0.002
LOG10VL		1.267	1.023-1.569	0.03
RISK GROUP				0.048
	MSM	1		
	HTSX	0.868	0.561-1.342	0.525
	IVDU	2.217	1.077-4.563	0.031
	OTHERS	0.445	0.136-1.456	0.181
ETHNICITY				0.142
	WHITE	1		
	BLACK	1.883	1.105-3.208	0.020
	HISPANIC	0.916	0.210-3.998	0.300
	OTHER	1.183	0.461-3.028	0.727
	UNKNOWN	0.594	0.344-1.026	0.261

Table 8. HIV viral load (categorized) at the end of follow-up.

	<20 COP/ML	20-50 COP/ML	51-200 COP/ML	>200 COP/ML
GENVOYA	141	48	19	5
TRIUMEQ	251	78	22	8
P VALUE				0.621

Table 9. Summary results with VL (>50) included as an AO.

	AO	NO AO
GENVOYA	60	153
TRIUMEQ	87	272
P VALUE		0.323

CONCLUSIONS:

Genvoya and Triumeq have become the preferred treatment combinations for the initiation or antiretroviral treatment in the VACH Cohort-associated hospitals in recent years (data not shown). Their use has been associated with a high and comparable degree of effectiveness.