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ORIGINALES

Efficacy and safety in real clinical conditions of Raltegravir in a reference hospital of peruvian social security

Eficacia y seguridad en condiciones clínicas reales del raltegravir en un hospital de referencia del seguro social peruano

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ABSTRACT:

Introduction: Rategravir belongs to integrase inhibitors, being demonstrated and approved by several clinical trials as a powerful and safe antiretroviral drug for the treatment of patients infected with human immunodeficiency virus (HIV), with good tolerance and low toxicity, including in the third line or rescue scheme and it starts when the first and second lineas schemes have failed.
Objective: To evaluate the efficacy and safety in real clinical conditions of the use of Raltegravir within the HAART schemes in patients with HIV infection in a reference hospital of social insurance in Peru.
Methods: A retrospective observational study was performed in patients with a diagnosis of HIV infection who started treatment within the TARGA scheme based on Raltegravir with follow-up and control at 6 months. We presented summary measures of frequencies and percentages for the qualitative variables, as well as means and standard deviation for the quantitative variables based on the results of the normality tests. The data was processed and analyzed in the statistical software SPSS version 22.
Results: The male gender was the most affected with 76% (n = 119) of the total. The most frequent age range was between 45 to 55 years (25.4%, n = 40). The most frequent comorbidities were Diabetes mellitus and arterial hypertension, with exponential reduction in viral load and elevation of CD4 lymphocyte levels.
Conclusion: Raltegravir is effective for the treatment of HIV patients.

Keywords: Anti-HIV drugs; HIV infections; raltegravi

RESUMEN:
Introducción: El Rategravir pertenece a los inhibidores de integrasas, quedando demostrado y aprobado por diversos ensayos clínicos como un potente antirretroviral seguro y eficaz para el tratamiento de pacientes infectados con el virus de inmunodeficiencia humana (VIH), con buena tolerancia y baja toxicidad, incluyéndose en el esquema de tercera línea o rescate y se inicia cuando los esquemas de primera y segunda línea han fracasado.
Objetivo: Evaluar la eficacia y seguridad en condiciones clínicas reales del uso de Raltegravir dentro de los esquemas de la Terapia Antiretroviral de Gran Actividad (TARGA) en pacientes con infección por VIH en un hospital de referencia del seguro social en Perú.
Métodos: Se realizó un estudio observacional retrospectivo en pacientes con diagnóstico de infección por VIH que iniciaron tratamiento dentro del esquema TARGA basados en Raltegravir con seguimiento y control a los 6 meses. Se presentaron medidas de resumen de frecuencias y porcentajes para las variables cualitativas, así como medias y desviación estándar para las variables cuantitativas en base a los resultados de las pruebas de normalidad. Los datos fueron procesados y analizados en el software estadístico SPSS versión 22.
Resultados: El género masculino fue el más afectado con un 76%(n=119) del total. El rango de edad más frecuente fue el comprendido entre los 45 a 55 años (25,4%; n=40). Las comorbilidades más frecuentes fueron Diabetes mellitus e Hipertensión arterial, con reducción exponencial de la carga viral y elevación de los niveles de linfocitos CD4.
Conclusión: El Raltegravir es eficaz para el tratamiento de pacientes VIH.

Palabras clave: Fármacos anti-VIH; infecciones por VIH; raltegravir

INTRODUCTION

In October 2007, integrase inhibitors (Iint) were approved for the treatment of patients infected with the human immunodeficiency virus (HIV), with Raltegravir being the first of them[(1)]. This drug was shown in different phases of clinical trials to be safe and effective with a powerful antiretroviral action, more effective than protease inhibitors (PIs) [(2)].

Since its approval, Raltegravir has shown adequate safety and efficacy for the treatment of HIV infection, as well as good tolerance by patients regardless of gender and race [(3)]. The toxicity and interaction with other anti-retroviral drugs are low because it is not metabolized within the cytochrome P450 system [(2)]. However, among the adverse effects are metabolic alterations such as blood lipid disorders among others[(4)].

According to the Peruvian technical standard, Raltegravir is included in the third-line or rescue therapy scheme and is started when the first and second-line highly active anti-retroviral treatment (HAART) schemes have failed to control the disease [(5)].

A study accomplished in a social security referral center in Peru determined that the proportion of patients who respond adequately to the Raltegravir-based treatment scheme is high and safety is acceptable. Despite this, the information about its safety and efficacy in real clinical conditions and especially in our population is still limited, despite the experience obtained since its prescription began in our center in 2007.

The objective was to describe the efficacy and safety in real clinical conditions of the Raltegravir-based HAART regimens in a series of patients with HIV infection in a social security referral hospital in Peru.

METHODS AND PROCEDURES

Retrospective observational study in HIV-infected patients who received Raltegravir-based HAART with follow-up and control in the infectious disease service of the national hospital "Edgardo Rebagliati Martins" -EsSalud, Lima-Peru in 2018.

Selection criteria

Those patients with a diagnosis of HIV infection who started in our center HAART based on Raltegravir and who also had follow-up and control at 6 months were included. Those patients with incomplete, illegible, or unavailable medical records at the time of their request and those who did not have a viral load or CD4 studies during the months of follow-up, as well as incomplete complementary laboratory tests (serum glucose, serum lipids, blood complete and liver profile), were excluded.

Ethical aspects

The confidentiality of the data was kept and protected, all participants had the right to anonymity. No experiments were performed on the patients and the ethical principles for research in humans stipulated in the Declaration of Helsinki were followed.

Population and sample size

All those who started Raltegravir-based HAART and controls in the infectology service of our hospital were included.

The effectiveness of Raltegravir-based HAART was defined as the presence of a viral load <1000 copies/ml at 6 months (24 weeks) of treatment and safety as the presence of mild or absent adverse drug reactions. Additionally, the following clinical variables were analyzed: Sex, age, comorbidities, number of years with diagnosis, usual medication, reason for using Raltegravir, HAART regimen based on Raltegravir received, CD4 level, hemogram, liver profile, lipid profile, glycemia, and serum creatinine.

The data were collected from clinical records using a data sheet prepared based on the objectives of the study. Viral load was determined using the PCR method in the HIV Architec (Roche®) equipment. CD4 levels were measured by flow cytometry on the BDFACS Canto II equipment. The complete blood count and biochemical analyzes were processed in the SYSMEX 2000 and ADVIA 1800 equipment, respectively.
Follow-up time: From the start of treatment to 6 months (24 weeks).

Statistical analysis

Summary measures of frequencies and percentages were presented for the qualitative variables, as well as means and standard deviation for the quantitative variables based on the results of the normality tests. The data were processed and analyzed in the statistical software SPSS version 22.

RESULTS

A total of 216 clinical records were located, of which 59 were excluded for not having viral load or CD4 controls, finally including only 157 records.

The gender most affected was male, representing 76% (n = 119) of the total. The most frequent age range was between 45 to 55 years (25.4%; n = 40). The two most frequent comorbidities were diabetes mellitus and arterial hypertension (24%; n = 14 and 17%; n = 10), with co-infection with hepatitis C being less frequent (2%; n = 1). Table 1 shows the general characteristics of the participants.

Table 1. General characteristics of patients undergoing treatment with Raltegravir.

		n	%
Age			
	15-25	3	1.91
	26-35	26	16.56
	36-45	36	22.93
	46-55	40	25.48
	56-65	34	21.66
	66-75	14	8.92
	<75	4	2.55
Sex			
	Female	38	24
	Male	119	76
Years diagnosed with HIV infection			
	< 5 years	30	19.11
	5-10 years	38	24.20
	10-15 years	19	12.10
	15-20 years	50	31.85
	> 20 years	20	12.74
Comorbidities			
	Diabetes Mellitus	14	23.73
	Arterial hypertension	10	16.95
	Chronic kidney disease	8	13.56
	Solid organ neoplasm	5	8.47
	Kaposi's sarcoma	4	6.78
	Hematological neoplasm	3	5.08
	HTLV	2	3.39
	Tuberculosis	6	10.17
	Hepatitis B	6	10.17
	Hepatitis C	1	1.69

Usual Medication				
		Statins	19	35.85
		Fibrates	26	49.06
		Statin plus fibrate	3	5.66
		Rifampicin	5	9.43
Reason sor using raltegravir				
	Naive			
		Tuberculosis	3	1.91
		Neoplasm	3	1.91
		Hepatitis B	2	1.27
		Hepatic cirrhosis	2	1.27
		Protocolo	1	0.64
		Other causes	2	1.27
		Does not specify	3	1.91
		Subtotal	16	10.19
	Toxicity			
		Pregnancy	1	0.64
		Dyslipidemias	6	3.82
		Cardiovascular risk	4	2.55
		Psychiatric risk	3	1.91
		Oral intolerance	4	2.55
		RAM EFV	5	3.18
		Nephrotoxicity	1	0.64
		Subtotal	33	21.02
	Virological failure			
		With resistance test	77	49.04
		No resistence test	25	15.92
		Sub Total	102	64.97
	Lack of medication		2	1.27
	Protocol		2	1.27
	Not specified		2	1.27

Viral load decreased exponentially, from 23 patients who presented undetectable viral load at the start of treatment, it increased to 145 patients after 6 months of treatment (Figure 1). Similarly, CD4 lymphocyte levels increased after 6 months of treatment (Figure 2). Concerning safety, an increase in the number of cases of patients with elevated serum glucose and creatinine was found (Table 2).

Figure 1. Efficacy of Raltegravir at 24 weeks of treatment

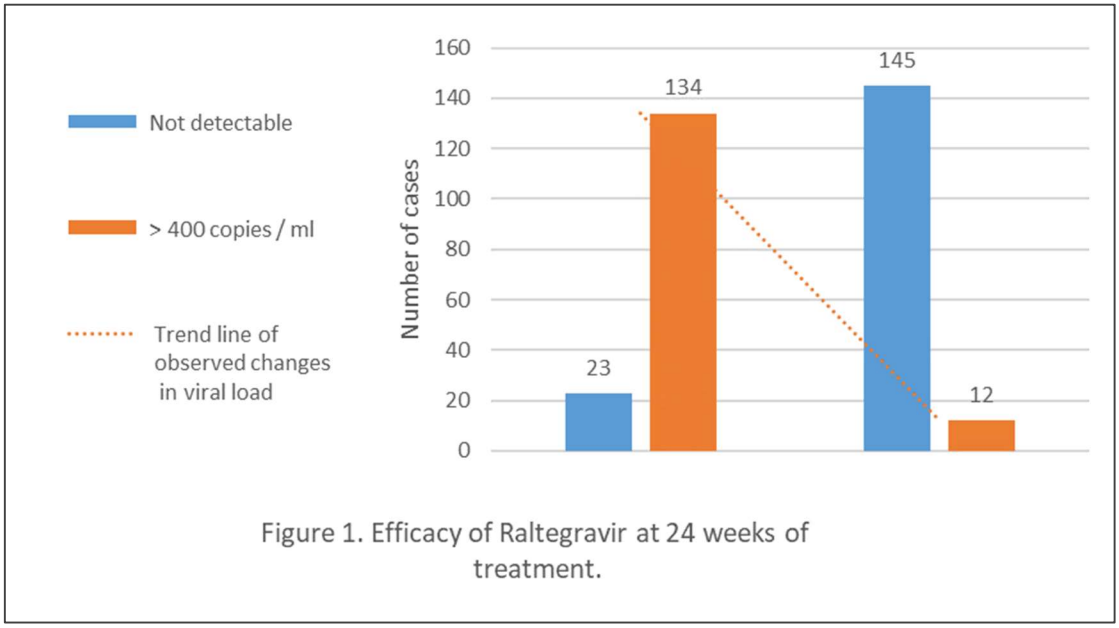

Figure 1. Efficacy of Raltegravir at 24 weeks of treatment.

Figure 2. CD4 lymphocyte levels before and 6 months of treatment

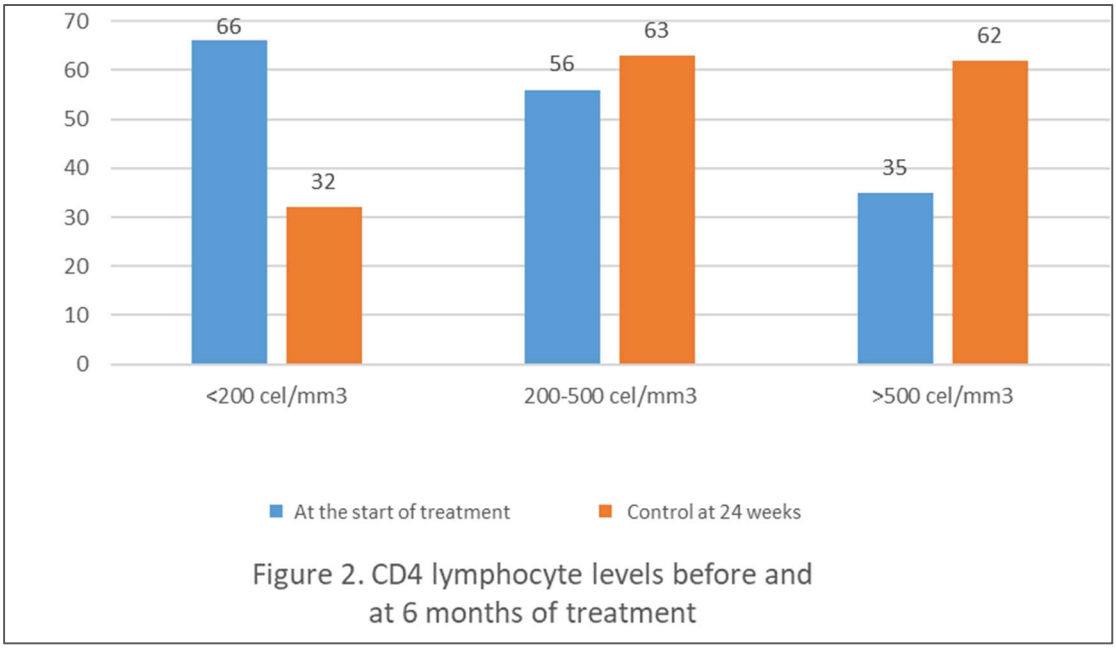

Figure 2. CD4 lymphocyte levels before and at 6 months of treatment

Table 2. Effect of Raltegravir on viral load, CD4 level, blood count and biochemical parameters

		At the start of treatment		Control at 24 weeks	
		n	%	n	%
HEMOGRAM AND BIOCHEMISTRY SERICA					
Hemoglobin					
	Males (Hb<13 g/L)	40	25.48	13	8.28
	Females (Hb<12 g/L)	15	9.55	9	5.73
Neutropenia (Absolute neutrophils)	Mild (1 - 1.5)	17	10.83	4	2.55
	Moderate (0.5 - 1)	6	3.82	0	0.00
	Severe (<0.5)	1	0.64	2	1.27
Absolute platelets	< 150 000	10	6.37	1	0.64
Serum glucose level					
	> 106 mg/dl	16	10.19	26	16.56
Creatinine level					
	Males (Cr>1.1 mg/dl)	9	5.73	13	8.28
	Females (Cr> 0.8 mg/dl)	7	4.46	5	3.18
Liver Profile					
	TGO> 34 mg/dl	40	25.48	28	17.83
	TGP> 49 mg/dl	29	18.47	23	14.65
	FA> 129 mg/dl	48	30.57	40	25.48
	BT> 1.2 mg/dl	9	5.73	7	4.46
	BD> 0.3 mg/dl	8	5.10	13	8.28
	BI> 0.5 mg/dl	15	9.55	12	7.64
Lipidic profile					
	Total cholesterol > 200 mg/dl	38	24.20	43	27.39
	HDL< 60 mg/dl	127	80.89	113	71.97
	LDL> 100 mg/dl	68	43.31	71	45.22
	Col/HDL > 5	42	26.75	49	31.21
	Triglycerides> 250	34	21.66	34	21.66

Note: Hb: Hemoglobin; Cr: serum creatinine; TGO: Transglutaryl oxamia; TGP: Trasglutarioapeptidase; FA: alkaline phosphatase; BT: Total bilirubin; BD: direct bilirubin; BI: Indirect Bilirubin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

DISCUSSION

The HAART regimens based on Raltegravir included in the study show a significant antiretroviral effect, which is reflected in the significant reduction in viral load at 6 months of treatment. Accordingly, various studies that have evaluated the efficacy of

regimens based on this drug in real clinical conditions have shown high efficacy for virus control [4,6,7]. However, the data is still limited, especially in our population[8].

Malpartida et al, in a retrospective study accomplished in a reference hospital similar to ours, a virological response of 90% was found compared to the 77.7% found in our study [9]. This difference is probably due to variables that we have not been able to control, nonetheless, it continues to represent a high efficacy for the control of the disease.

In a Mexican multi-center cohort, they evaluated the effectiveness and risk factors for the virological outcome of HAART regimens based on Raltegravir plus an optimized additional regimen in patients who had received HAART. High virological suppression rates were found at 48 weeks of treatment similar to ours. On the other hand, age over 40 years was associated with a good virological result with a significant effect size (Odds Ratio [OR]: 5.61; 95% Confidence Interval [95% CI]: 1.61- 18.84), however, the use of Tenofovir within the regimen was associated with a poor virological outcome (OR: 0.16; 95% CI: 0.03-0.80) [7].

Similarly, in another, they evaluated the efficacy of Raltegravir-based HAART regimens under real-world clinical conditions in new and previously treated patients. The schemes showed adequate long-term efficacy. In both groups, virological suppression was obtained and maintained at 24 weeks of treatment in a high percentage and this suppression was maintained until the end of follow-up (48 weeks)[8]. It has also been observed that HAART regimens based on Raltegravir in patients over 60 years of age are safe and highly effective. Furthermore, in this population, it is associated with a reduction in triglyceride and platelet count [10]. These results are consistent with what was reported in the different clinical trials carried out prior to their approval [2].

Based on all of them, regimens based on Raltegravir in real clinical practice show adequate efficacy for reducing viral load, a control with an important effect that can be observed 6 months after starting treatment. Its long-term use could have good tolerability and efficacy since it has been shown that long-term use continues to present adequate margins of safety and efficacy.

Regarding the safety margin, it is one of the best tolerated anti-retroviral drugs with limited adverse effects and minimal drug interactions [10]. We report an increase in the number of cases of patients with elevated serum levels of serum glucose and creatinine. In contrast, in patients older than 60 years, a reduction in the triglyceride count and the number of platelets is observed [10]. These changes in glycemia are probably due to the comorbidities that patients presented at the beginning of treatment. The most frequent comorbidity was diabetes mellitus and as there was no adequate control over its influence on laboratory results and follow-up, it may have been associated with alterations in the results observed in its controls.

Among the reasons for the use of Raltegravir, the most frequent was the failure of viral control by previously used HAART regimens.

Limitations

The most important limitation was the impossibility of controlling for a great variety of possible variables that intervened and that probably modified the patients' response to the drug. However, the exponential drop in viral load reveals the important antiretroviral effect of the drug, which appears to be independent of the effect of some additional variable.

CONCLUSION

HAART regimens based on Raltegravir in real clinical conditions are safe and effective for the control of HIV. This drug has a powerful antiretroviral action and the effects can be seen 6 months after starting treatment. It must be used rationally and prescribed with caution. This drug should be reserved for the most severe cases and with the failure of the first and second-line regimens.

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