

EFFECTIVENESS AND SAFETY OF SALVAGE THERAPY ON ROMANIAN HIV INFECTED PATIENTS

MANUELA ARBUNE¹, COSTINELA GEORGESCU^{2*}, MAGDALENA CUCIUREANU³, MICHAELA DOBRE⁴

¹*Clinical Department, Faculty of Medicine and Pharmacy, „Dunarea de Jos” University of Galati, 35, Al. I Cuza Street, Galati, Romania*

²*Department of Pharmaceutical Sciences, Faculty of Medicine and Pharmacy, „Dunarea de Jos” University of Galati, 35, Al. I Cuza Street, Galati, Romania*

³*Department of Pharmacology, Faculty of Medicine, "Gr. T. Popa" University of Medicine and Pharmacy, 16, Universitatii Street, Iasi, Romania*

⁴*Department of Functional Sciences, Faculty of Medicine and Pharmacy, „Dunarea de Jos” University of Galati, 35, Al. I Cuza Street, Galati, Romania*

**corresponding author: costinelag@gmail.com*

Abstract

Long life antiretroviral treatment (ART) is crucial for surviving of patients infected with human immunodeficiency virus (HIV), but the efficacy and durability of this therapy is compromised by the emerging of drug resistance. Patients with more than two therapy failure are difficult to treat because of frequent drugs cross-resistance. Salvage therapy supposes new agents with different mechanisms of viral action or with improved pharmacological characteristics and represents a viable treatment option after multiple therapeutic failures. A prospective observational study was conducted on a group of 13 heavily experienced HIV Romanian young adults who were treated with raltegravir, etravirine and ritonavir boosted darunavir for 96 weeks. The average gain of LCD4 (log cluster of differentiation 4 count) was 261/mm³ and full viral replication suppression was achieved in 8 out of 10 patients. In conclusion, our results show that the use of salvage ART is considered efficient and safe.

Rezumat

Supraviețuirea pacienților infectați cu virusul imunodeficienței umane (HIV) depinde de administrarea terapiei antiretrovirale (ART) pe durata întregii vieți, dar eficiența și durabilitatea medicației pot fi compromise din cauza apariției rezistenței virale. Alegerea schemei terapeutice este dificilă în cazul pacienților care au înregistrat mai mult de două eșecuri terapeutice, din cauza rezistenței încrucișate în cadrul aceleiași clase de medicamente. Terapiile de salvare la pacienții expuși la multiple ART necesită noi agenți terapeutici, cu mecanisme de acțiune diferite sau cu proprietăți farmacocinetice îmbunătățite față de cele folosite anterior. Studiul nostru a evaluat prospectiv timp de 96 de săptămâni rezultatele administrării terapiei de salvare cu raltegravir, etravirină și darunavir asociat cu ritonavir, la treisprezece tineri cu infecție HIV expuși la multiple ART. Răspunsul imunologic la terapie a fost creșterea medie a numărului LCD4 cu 261/mm³, concomitent cu supresia replicării virale la 8 din 10 pacienți. În concluzie, rezultatele noastre indică faptul că terapia de salvare prezintă eficiență și siguranță.

Keywords: HIV, raltegravir, etravirine, darunavir, Romanian patients

Introduction

The characterization of the human immunodeficiency virus (HIV) as a retrovirus possessing structural proteins and enzymes capable of performing the viral life cycle (reverse-transcriptase, protease, integrase) enabled the development of antiretroviral drugs. Unfortunately, no cure for HIV is yet available, but highly active combinations of antiretroviral HIV medication (ART) decreased mortality and transformed a fatal disease into a chronic disease. Nowadays, there are 30 standalone or combined medication protocols licensed for HIV treatment. Among the most important ART classes it is worth mentioning: nucleoside or nucleotide reverse-transcriptase inhibitors (NRTI), non-nucleoside reverse-transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (II), entry inhibitors including chemokine co-receptor antagonists (CCR) and fusion inhibitors (FI) [10,14].

NRTI and NNRTI are analogues that inhibit reverse transcriptase, thereby impairing viral replication and incorporation into the host cell genome [1,19,20]. Protease inhibitors (PIs) hinder the active protease site and block the cleavage of the HIV polyprotein precursor, producing non-infectious viruses [11]. The availability and effectiveness of PIs are improved by pharmacokinetic “boosting”, i.e. adding low doses of ritonavir (RTV). The CYP3A4 enzyme is inhibited by RTV and increases the peak concentration and the half-life of PI [21]. Integrase inhibitors (II) competitively bind the metallic ions at interface’s active sites and thus inactivate the enzyme. By blocking the transport and attachment of proviral DNA to host-cell chromosomes, they impair the transcription of viral proteins and the subsequent assembly of virus particles [3].

The main target of ART is full viral suppression with undetectable blood viral loads (ARN-HIV) and regain of immune function through increasing the number of LCD4 lymphocytes. Unfortunately, the high HIV replication rate and suboptimal exposure to the antiretroviral drugs facilitate viral mutations and subsequent drug resistance. A strategy to fight emerging resistance is to “hit” multiple viral targets by combining more than three antiretroviral drugs. Standard first line antiretroviroal therapy includes at least three antiretroviral (ARV) drugs, two of which are NRTIs and one is either NNRTI or boosted protease inhibitor (PI). However, multiple therapeutic failures and drug resistance in antiretroviral naive patients demand for new potent drugs combinations. The salvage therapy comes into consideration after two failures of antiretroviral classes [8,10].

Materials and Methods

This study assessed the efficacy and safety of a salvage therapy comprising new drugs: raltegravir (RAL), etravirine (ETV) and darunavir/ritonavir (DRV/RTV), over a period of 96 weeks, and to subsequently compare our results with those of TRIO reference study [7].

A prospective observational study was conducted on a group of heavily experienced HIV patients who were admitted to Infectious Diseases Hospital, Galati, Romania and who were treated with raltegravir (RAL), etravirine (ETV) and darunavir/ritonavir (DRV/RTV). The investigation ended after 96 weeks of treatment or whenever a patient's treatment had to be prematurely ceased, regardless of motivation.

This study was approved by the Ethical Committee of the 'Dunarea de Jos' University and the Infectious Diseases Hospital of Galati and was carried in accordance with standard operation procedures ensuring Good Clinical Practice Guidelines. Written informed consent was obtained from all the subjects before admission to the study.

In order to be eligible for the study each subject had to meet the following inclusion criteria: HIV-viral load above 1000c/mL, more than two antiretroviral failures that included at least one NNRTI and one PI but didn't include RAL, ETV and DRV/RTV, age between 18 and 25, more than 5 years since HIV diagnostic, history of AIDS defining clinical or immunological events and stable clinical status with no active opportunistic infections or cancers. It was also required that the patients exhibit both susceptibility to darunavir (less than 3 from the following mutations: V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V) and to etravirine (less than 3 from the following NNRTI mutations: A98G, L100I, K101Q/P/E, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179D/E/F/G/I, Y181C/I/V/C/H/L, Y188C/H/L, G190A/C/E/Q/S, P225H, F227C/L, M230I/L, P236L, K238N/T and Y318).

The exclusion criteria included the evidence of non-adherent behaviour, severe adverse effects associated with the discontinuation of the therapy and the administration of any systemic medication that interferes with ART.

Medication was supplied through the Romanian National HIV/AIDS Programme and was dispensed on a monthly basis by the Pharmacy of the HIV/AIDS Clinic of Galati. The drugs were self-administered orally every 12 hours as follows: one 400-mg tablet of raltegravir, two 100-mg tablets of etravirine and two 300-mg/100-mg tablets of darunavir/ritonavir.

The efficiency of ART was evaluated considering clinical, immunological and virological criteria - the absence of AIDS-defining

clinical events, an increase of the LCD4 (log cluster of differentiation 4 count) and the achievement of full viral suppression with undetectable HIV blood viral load.

LCD4 count, HIV viral load measurements and the genotypic resistance testing were performed in the Laboratory of Infectious Diseases, “Matei Bals” Institute, Bucharest on study weeks 0, 24, 48 and 96.

Results and Discussion

Out of the 252 patients receiving ART through the HIV/AIDS Clinic of Galati, 13 patients (5%) were enrolled for the clinical trial. The study population comprised 7 males (53.84 %) and 6 females (46.15 %) with a mean age of 21 years [20; 24]. The majority of the study population was living in urban area (61.53 %) whereas 5 patients (38.46%) were from the rural area. The average length since HIV diagnostic was 13.2 years [6;18]. 76.92% of the study population (10 patients) experienced specific clinical AIDS events and 84.61% recorded CD4 count less than 200 cells/mm³. Co-infections with hepatitis B virus were evidenced in 3 cases, but none HCV (hepatitis C) was found. In terms of level of education, 9 out of 13 subjects had graduated high school and all reported having stable housing. All study participants were white Caucasians and had a Body Mass Index (BMI) between 19 and 26.

Three patients were excluded from the study before 96 weeks: one in the first month, due to a severe allergy to ETV, and two others because of ETV and DRV/RTV cross-interactions with rifampicine, administered for tuberculosis treatment between weeks 24 and 96.

The immunological state was significantly improved under treatment, as shown by a progressive increase of LCD4 by an average of 166/mm³ at 24 weeks, 261/mm³ at 48 weeks and 266/mm³ at 98 weeks (Figure 1).

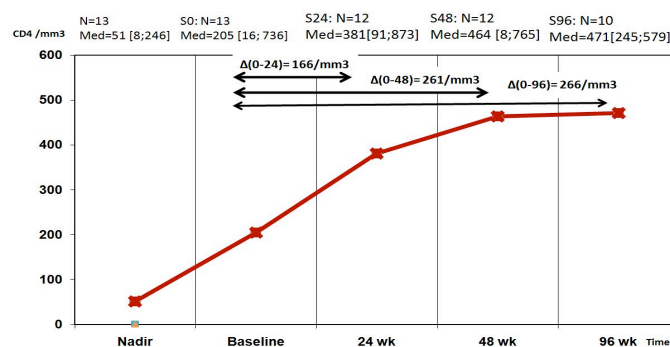


Figure 1

Median LCD4 count evolution under RAL+ETV+DRV/RTV treatment

The HIV viral load dropped to undetectable in 9 out of 12 patients after 24 weeks of treatment. The ratio of patients with full viral suppression was relatively stable between 24 and 96 weeks (8 out of 11 patients after 48 weeks and 8 out of 10 patients after 96 weeks – Figure 2)). Patients with detectable viral load in 24 weeks continued the decreasing trend of HIV viral load until week 96.

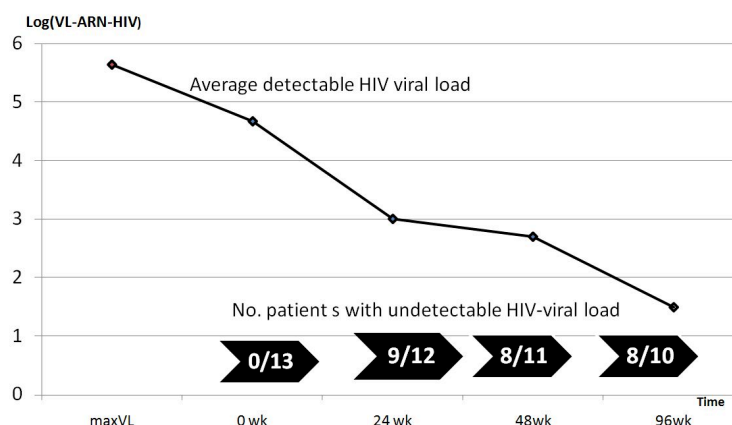


Figure 2

The evolution of HIV- viral load under RAL+ETV+DRV/TRV treatment

With the exception of one patient experiencing a severe rash that lead to treatment discontinuation in the first month, mild clinical adverse events such as headaches, abdominal pain, diarrhea, or rashes were reported in 8 out of 13 patients. Mild increases of cholesterol and triglyceride levels were reported in two cases. Two cases of tuberculosis were diagnosed after 24 weeks since the beginning of the study, and the subjects were withdrawn from the study. There was no evidence of other clinically significant cardiovascular, renal, hepatic, hematological, gastrointestinal, neurological events or other major diseases.

HIV patients heavily experienced with ART are difficult to treat because of cross-resistances developing between antiretroviral drugs belonging to the same class. New drugs like DRV and ETV have the benefit of different resistance patterns and higher genetic barriers compared to other PIs and NNRTIs, respectively. Furthermore, RAL is the first antiretroviral agent belonging to the II class [6].

The metabolism of RAL by uridine diphosphate-glucuronosyl-transferase is not influenced by the co-administration of ETV, RTV and DRV. Therefore, the combination of these drugs is not limited by pharmacokinetic interactions [5].

The drugs included in this study, RAL, ETV and DRV were available in our clinic from 2009, but pricing made the prescription prohibitive [4,15]. The cost of a RAL+ETV+DRV/RTV treatment course was at the end of 2012 more than three times higher than the national average monthly cost per patient receiving antiretroviral treatment [23].

Regarding the two cases of dropouts after 24 weeks of treatment, we have to take into consideration the fact that the region itself has a high prevalence of tuberculosis even in the general population. Rifampicin administered for tuberculosis treatment and DRV/RTV are metabolic competitors, both requiring CYP3A4. Moreover, literature data indicate that ETV should not be combined with anti-tuberculosis drugs [2]. Furthermore, analogous increases of cholesterol levels as we found in our study were identified in other rescue regimens for multidrug-resistant HIV-1 infection [15].

It is also important to point out that recent data show that the results of the salvage therapy are not influenced by HBV co-infection. Weimer *et al.* indicated that, in these cases, drug-induced hepatotoxicity is not associated with higher risk of withdrawal [22].

The combination of RAL+ETV+DRV/RTV was also evaluated by an ANRS 139 TRIO trial, which was conducted on 103 participants for a period of 96 weeks [7]. The rate of achievement of an undetectable HIV viral load for our patients (8 out of 13 patients representing 61.53%) was lower than the rate of 88% found in the TRIO trial at the end of week 96. However, CD4 response was superior in our patients as compared to the TRIO study, both at 24 weeks (166 cells/mm³ *versus* 108 cells/mm³) and at 96 weeks (261 cells/mm³ *versus* 149 cells/mm³). The differences in therapeutic response should also be viewed in light of the younger age of our patients relative to the TRIO study (mean age of 21 *versus* mean age of 45 years).

A similar study using the same drugs but in higher doses - RAL (400 mg twice daily), ETR (200 mg twice daily), and DRV/RTV (600/100 mg twice daily) - showed that 94% of patients with a median age of 44 achieved HIV1-RNA less than 50 copies/mL after 24 weeks of treatment. Even if in this study the rate of achievement of an undetectable HIV viral load was significantly superior to the ratio we have obtained, the immunological response was less important (103 cells/mm³ as compared to 166 cells/mm³) [12].

Our data are in agreement with literature data which indicate that younger patients have a better outlook for immune recovery after salvage therapy [17]. On the other hand, an increased length of time since HIV

diagnosis and an extended period of treatment might negatively impact adherence and explain the higher frequency of cases with detectable HIV viral loads [9].

A new trend for optimizing ART in countries with limited financial resources and no access to genotyping is the use of computational models in order to predict response to HIV therapy [18]. Highly individualized and personalized antiretroviral regimes can achieve significant benefits in heavily experienced HIV patients with multiple class resistance [13].

Conclusions

Our results show that the use of salvage ART composed of raltegravir, etravirine and ritonavir-boosted-darunavir can be considered efficient and safe. As compared to another literature TRIO, our study is characterized by the inclusion of young age heavily experienced HIV patients who exhibited a better immunological recovery after 96 weeks of salvage treatment.

References

1. Ammaranond P., Sanguansittianan S., Mechanism of HIV antiretroviral drugs progress toward drug resistance. *Fundamental & Clinical Pharmacology*. 2012; 26: 46–161.
2. Brown KC, Sunita P, Kashuba A. Drug Interactions with New and Investigational Antiretrovirals: darunavir, etravirine, rilpivirine (TMC278), maraviroc, vicriviroc, raltegravir, elvitegravir, INCB 9471 (CCR5), bevirimat. *Clinical Pharmacokinetics*. 2009; 48(4): 211-241.
3. Craigie R. HIV integrase: a brief overview from chemistry to therapeutics. *J Biol Chem*. 2001; 276:23213-23216.
4. Crisan O. Les droits de patients en Roumanie: le droit a la qualite des soins et l'exercice des droits par les patients. *Farmacia*, 2012, 60(1): 138-142.
5. Croxtall JD, Lyseng-Williamson KA, Perry CM. Raltegravir. *Drugs*. 2008; 68:131-138.
6. Eron JJ. Managing antiretroviral therapy: changing regimens, resistance testing, and the risks from structured treatment interruptions. *J Infect Dis*. 2008; 197(S3):S261-S271.
7. Fagard C, Colin C, Charpentier C, et al. Long-Term Efficacy and Safety of Raltegravir, Etravirine, and Darunavir/Ritonavir in Treatment-Experienced Patients: Week 96 Results From the ANRS 139 TRIO Trial. *J. Acquir Immune Defic Syndr*. 2012; 59(5): 489-493.
8. Hertogs K, Bloor S, Kemp S, et al. Phenotypic and genotypic analysis of clinical HIV-1 isolates reveals extensive protease inhibitor crossresistance: a survey of over 6000 samples. *AIDS*. 2000; 14:1203–1210.
9. Hinkin CH, Hardy DJ, Mason KI, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS*. 2004; 18(S1): S19-25.
10. Hoffmann Ch., Rockstroch J. HIV 2012/2013. Medizin Fokus Verlag, 2012, Hamburg: 60-254.
11. Huff J.R., Kahn J. Discovery and clinical development of HIV-1 protease inhibitors. *Adv. Protein Chem*. 2001, 56, 13–251.
12. Imaz A, del Saz SV, Ribas MA, Curran A, Caballero E, Falcó V, Crespo M, Ocaña I, Diaz M, de Gopegui ER, Riera M, Ribera E., Raltegravir, etravirine, and ritonavir-boosted darunavir: a safe and successful rescue regimen for multidrug-resistant HIV-1 infection. *J Acquir Immune Defic Syndr*. 2009; 52(3):382-6.

13. Jensen B, Esser S, Kaiser R, Luebke N, Häussinger D. How individual can personalized antiretroviral treatment be? Deep salvage in an HIV-1-infected patient. *Intervirolgy*.2012; 55(2),167-71.
14. Patel I, Zhang X, Nieforth K, Salgo M, Buss N. Pharmacokinetics, pharmacodynamics, and drug interaction potential of enfuvirtide. *Clin Pharmacokinet*. 2005; 44:175-186.
15. Patterson P, Magneres C, Sued O, Fink V, Figueroa M, Cesar C, Gun A, Cahn P, Krolewiecki A. A phase 4, single-arm, open-label, pilot study of maraviroc, raltegravir and darunavir/r in HIV-1 adults with triple classfailure: TERCETO study. *J Int AIDS Soc*. 2012; 15(6):18268.
16. Purcarea VL, Bolocan A, Paduraru DN. The evolution of the Romanian pharmaceutical market throughout the last great recession. *Farmacia*, 2012; 60(3):307-314.
17. Rakhmanina N, Anker J, Baghdassarian A, Soldin S, Williams K, Neely M. Population Pharmacokinetics of Lopinavir Predict Suboptimal Therapeutic Concentrations in Treatment-Experienced Human Immunodeficiency Virus-Infected Children. *Antimicrob Agents Chemother*. 2009; 53(6): 2532-2538.
18. Revell A, Wan, D, Alvarez-Uria G *et al*. Computational models that predict response to HIV therapy can reduce virological failure and therapy costs in resource-limited settings. *JIAS*. 2012, 15(Suppl 4):18114.
19. Seckler JM, Howard KJ, Barkley MD, Wintrod PL. Solution structural dynamics of HIV-1 reverse transcriptase heterodimer. *Biochemistry*. 2009; 48:7646–7655.
20. Sluis-Cremer N, Temiz NA, Bahar I. Conformational changes in HIV-1 reverse transcriptase induced by nonnucleoside reverse transcriptase inhibitor binding. *Curr HIV Res*. 2004; 2: 323-332.
21. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. *J Antimicrob Chemother*. 2004; 53(1): 4-9.
22. Weimer LE, Fragola V, Floridia M, Guaraldi G, Ladisa N, Francisci D *et al*. Response to raltegravir-based salvage therapy in HIV-infected patients with hepatitis C virus or hepatitis B virus coinfection, *J Antimicrob Chemother*. 2011; 68(1):193-9.
23. Ordinul MS/CNAS 1591/1110 din 30 decembrie 2010 pentru aprobarea Normelor tehnice de realizare a programelor naționale de sănătate pentru anii 2011 și 2012, Monitorul Oficial al României, Partea I, nr. 53/21.01.2011.

Manuscript received: February 5th 2013