Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.67663 • *J Pediatr Inf 2018;12(4):e135-e139*

The Safety and the Efficacy of First-line Antiretroviral Treatment Regimens in Children: A Single Center Experience in Turkey

Çocuklarda Birinci Basamak Antiretroviral Tedavi Rejimlerinin Güvenliği ve Etkinliği: Türkiye'de Tek Merkez Deneyimi

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Cite this article as: Kaba Ö, Hançerli Törün S, Kara M, Köksal MO, Ağaçfidan A, Somer A. The safety and the efficacy of first-line antiretroviral treatment regimens in children: a single center experience in Turkey. J Pediatr Inf 2018;12(4):e135-e139

Abstract

Objective: Active antiretroviral therapy refers to the use of a combination of drugs for treating human immune deficiency virus infection with the aim of preventing long-term toxicity.

Material and Methods: This study included 27 HIV-infected patients less than 18 years of age, between the years of 2001-2016. Primary outcomes were serious adverse events and virologic response to ART.

Results: The mean age of the patients at the time of diagnosis was 69.2 (1-204) months. Twenty-two patients had LPV/r-based regimen as first-line ART, initially. The mean follow-up period was 67.1 (6-192) months. First line therapy was changed in 6 patients. Resistance against antiretroviral drugs was found in four patients.

Conclusion: Despite small number of patients, a protease inhibitor-based regime seems to be a good option for children in immune recovery.

Keywords: Toxicity, pediatric, HIV, antiretroviral treatment, resistance

Öz

Giriş: Aktif antiretroviral tedavi insan immünyetmezlik virüsü (HIV) enfeksiyonunda uzun dönem toksisiteyi önlemek amacıyla ilaç kombinasyonunun kullanımını ifade eder.

Gereç ve Yöntemler: Bu çalışma 18 yaş altında olan ve 2001-2016 yılları arasında HIV ile enfekte olan 27 hastayı içermektedir. Birincil sonuçlar ciddi yan etkiler ve antiretroviral tedavi (ART)'ye virolojik yanıt idi

Bulgular: Tanı anında hastaların ortalama yaşı 69.2 (1-204) aydı. Yirmi iki hastada başlangıçta birinci basamak ART olarak LPV/r bazlı rejim kullanıldı. Ortalama takip süresi 67.1 (6-192) aydı. Altı hastada birinci basamak tedavi değiştirildi. Dört hastada antiretroviral ilaçlara karşı direnç saptandı.

Sonuç: Hasta sayısının azlığına rağmen; proteaz inhibitörünün baz alındığı rejimin immün yanıtı olan çocuklar için iyi bir seçenek olduğu düşünüldü.

Anahtar Terimler: Toksisite, pediatrik, HIV, antiretroviral tedavi, direnç

Introduction

The introduction of highly active antiretroviral therapy (ART) for human immune deficiency virus (HIV) infection has greatly improved the outcomes of children living with HIV around the globe. Antiretroviral therapy refers to the lifelong use of a combination of three or more antiretroviral (ARV) drugs for treating HIV infection. Clinicians should always consider nutritional status of the patients, presence of comorbidities and other medications in order to foresee possible

Received: 21.09.2018 **Accepted:** 27.11.2018

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interactions, contraindications and dose adjustment, before starting ART.

World Health Organization (WHO) guideline updates in 2016 suggests Lopinavir/ritonavir (LPV/r) based regimen {AZT(zidovudine) + 3TC(lamivudine) + LPV/r} as first-line ART for all children infected with HIV younger than 3 years of age, regardless of non-nucleoside reverse-transcriptase inhibitor (NNRTI) exposure (1). For children between 3 to 10 years of age, the nucleoside reverse-transcriptase inhibitors (NRTIs) are the backbone of the therapy. First-line ART for adolescents should consist of two NRTIs plus an NNRTI and fixed-dose combinations and/or once-daily regimens are preferred.

The management of ART is harder in children than adults since they are growing organisms and are more prone to long time toxic effects of these agents. Besides, drug formulations may always not be suitable for young infants and babies, thus ART should be individualized. In this study, we aimed to investigate safety and efficacy of first-line ART regimens in children and to address the long-term metabolic implications, in addition to virologic and immunological response.

Materials and Methods

This study is a clinical analysis of 27 pediatric patients diagnosed with HIV infection in our pediatric infectious disease clinic during a 14 year period from 2001-2016. For children ≥ 18 months, HIV infection diagnosis is based on positive HIV antibody testing confirmed by a second HIV antibody test and a positive virological test. HIV diagnosis is established by positive virological test for HIV or its components confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth for smaller children HIV-infected patients under 18 years were enrolled (2).

The charts of the patients were retrospectively scanned in order to gather epidemiologic, clinical and laboratory data, treatment modalities, treatment response, side effects, complications and outcomes. Laboratory investigations consisted of CD4 and CD8 counts, and polymerase chain reaction for HIV RNA from all participants. Monoclonal antibodies have been measured by four-color flow cytometry method (BD Facs Calibur, BD Calibur, BD Biosciences, San Jose, California, USA). Patient data were compared with reference values adjusted for age.

In our Microbiology Department, HIV RNA analysis was performed by the LCx HIV RNA Quantitative assay (Abbott Laboratories, North Chicago, III, US) with a dynamic measurement range < 178-5.011.872 copies/mL between 2001 and 2007, by an Artus HIV-1 QS-RGQ test (QIAGEN Ltd, Crawley, UK) with a dynamic measurement range < 72- 25.000.000 copies/mL from 2007 to 2010, and by COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 test 96 system (Roche Molecular Diagnostics, Basel, Switzerland) with a dynamic measurement range of 20-10.000.000 copies/mL since 2010.

Viral RNA isolation and RT-PCR of the PR and RT genes (PRRT) were performed as previously described, using the following primers PRRT-F, 50 -GAAGAAATGATGAC AGCATGTCAGGG-30 (nt 1819-1844) and PRRT-R, 50 -T AATTTATCTACTTGTTCATTTCCTCCAAT-30 (nt 4202-4173), and PRRT-2F, 50 -AGACAGGCTAATTTTTTAGG GA-30 (nt 2023-2045) and PRRT-2R, 50 -ATGGTTCTTGA TAAATTTGATATGTCC-30 (nt 3585-3559) for a nested PCR. The 1.5 kb PCR product was purified by Exo-SAP and sequenced as described (3).

Primary outcomes of interest included serious adverse events, virologic and immunologic response to ART. Serious adverse events were classified according to the Adverse Event Toxicity Scale (Division of AIDS 2004) as grade 1 to 4 (4). Using this scale, grade 1 and 2 denoted mild to moderate symptoms, grade 3 denoted serious symptoms and grade 4 denoted life-threatening events requiring significant clinical intervention.

Virologic response was accepted as the achievement of undetectable viral load. Immunologic response; we defined this as the meanchange in the concentration of CD4 lymphocytes from baseline, as expressed in cells/μL.

Secondary outcomes: Development of ART drug resistance was defined as acquisition of major genotypic resistance mutations. Minor mutations were not reported.

The study was approved by the institutional ethical review board (2017/1290).

Results

Twenty seven patients under 18 years of age admitted to Pediatric Infectious Disease Department between 2001-2016 were enrolled (Table 1). There were 15 males and 12 females with a male/female ratio of 1.2 to 1.

The mean age of the patients at the time of diagnosis was 69.2 (1-204) months. 44.4% of the patients were under 3 years of age, 37.1 % of them were between 3 to 10 years old and; and the remainder was (18.5 %) older than 10 years.

LPV/r-based regimen (AZT + 3TC + LPV/rb) as first-line ART was started in 22 patients (81.4%). A patient who was also infected with hepatitis B virus (HBV) received tenofovir alafenamide fumarate(TDF), 3TC and nevirapine (NVP) as first-line ART. Fixed dose combination therapy (Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine (FTC) 200 mg plus TDF 300 mg) was preferred in 2 children older than 15 years of age. A patient with intracranial thromboembolic attack was given AZT + 3TC + NVP combination, initially. The preferred first-line ART regimen was efavirenz (EFZ) + 3TC + AZT in a patient with lymphoma.

Table 1. Blood samples analyzed for immunologic, virologic response and toxicity of first line ART regime

Age at start of treatment (months)	ART regime	İmmunologic response	Virologic response	Toxicity	Antiviral resistance	Follow up period (months)	Recent ART regime
96	AZT + 3TC + LPV/rb	+	+	Anemia (Grade 4)	-	91	3TC + TDF + LPV/rb
72	TDF+3TC+NVP	+	+	-	-	72	Same
32	AZT + 3TC + LPV/rb	+	-	-	+[1]	60	AZT + TDF + LPV/rb
204	EVG + FTC + TDF	+	+	-	-	6	Same
4	AZT + 3TC + LPV/rb	+	+	-	-	108	Same
33	AZT + 3TC + LPV/rb	+	+	-	-	18	Same
1	AZT + 3TC + LPV/rb	+	+	-	+[2]	192	AZT + 3TC + RTV + DRV
108	AZT + 3TC + LPV/rb	+	+	-	-	108	Same
13	AZT + 3TC + LPV/rb	+	+	Neutropeni (Grade 2) Hyperamylasemia (Grade 2)	-	96	Same
24	AZT +3TC + LPV/rb	+	+	Vomiting (Grade 2)	-	120	Same
3	AZT + 3TC + LPV/rb	+	+	-	-	72	Same
96	AZT + 3TC + LPV/rb	+	+	-	-	60	Same
72	AZT + 3TC + LPV/rb	+	+	Vomiting (Grade 1)	-	48	Same
144	AZT + 3TC + LPV/rb	+	+	-	-	36	Same
8	AZT + 3TC + LPV/rb	+	+	-	-	132	Same
72	AZT + 3TC + LPV/rb	+	+	-	-	48	Same
144	AZT + 3TC + LPV/rb	+	+	Hyperlipidemia (Grade 2)	-	36	Same
60	AZT + 3TC + LPV/rb	+	+	Hyperlipidemia (Grade 2)	-	132	Same
180	EVG + FTC + TDF	+	+	-	-	7	Same
48	AZT + 3TC + LPV/rb	+	-	-	+[3]	72	AZT + TDF + LPV/rb
4	AZT + 3TC + LPV/rb	+	+	-	-	12	Same
24	AZT + 3TC + LPV/rb	+	+	Hyperamylasemia (Grade 2)	-	8	Same
34	AZT + 3TC + LPV/rb	+	+	-	-	109	Same
96	AZT + 3TC + LPV/rb	+	-	-	+[4]	48	3TC + EFV + DTG
33	AZT + 3TC + LPV/rb	+	+	-	-	96	FTC + TDF + DTG
72	AZT + 3TC + NVP	-	+	-	-	8	Ex[5]
180	EFV + 3TC + AZT	+	+	-	-	37	Ex[6]

[1] NRTI resistance mutations: M184V
[2] NRTI resistance mutations: D67N, T69NT, K70R, K219Q NNRT resistance mutations: A98G, Y181C PI gene mutations: 33F, I54V, V82A, L90M
[3] NRTI resistance mutations: A62AV, M184V NNRT resistance mutations: K103EK, V1061
[4] INT gene mutations: L68V, L74I PI gene mutations: M46Im, I47A, L10V, K20I, Q58EQ
[5] Ex due to intracranial tromboemboli.
[6] Ex due to invasive aspergillosis during bone marrow transplantation that was done for non-hodgkin lymphoma.
* AZT: Zidovudine, DRV: Darunavir, DTG: Dolutegravir, EFV: Efavirenz, FTC: Emtricitabine, EVG: Elvitegravir, LPV/r: Lopinavir/ritonavir, NVP: Nevirapine, TDF: Tenofovir alafenamide fumarate, 3TC: Lamivudine.

Immunologic/Virologic Response: One patient with clinical stage 3 disease who had diffuse intracranial thrombosis did not develop an immunologic response and 3 patients with antiviral resistance had no virologic response to LPV/rb first line ART.

Toxicity: Seven patients had eight toxicity symptoms. A patient who received AZT + 3TC + LPV/rb admitted to emergency department with severe anemia requiring transfusion. After elimination of possible infectious and hematologic causes, anemia was evaluated as a side effect of AZT. AZT was switched to TDF and the anemia disappeared.

Two patients who were using AZT + 3TC + LPV/rb, complained of vomiting; one of them had frequent vomiting episodes with no or mild dehydration and other had intermittent vomiting with no or minimal interference with oral intake. None of them required a change in therapy.

Laboratory tests showed elevation of amylase levels (1.6-2.0 x ULN) in two patients who treated with AZT + 3TC + LPV/rb, and one of these patients experienced neutropenia (800/mm^3). In other two patients, it was shown that the low density lipoprotein cholesterol (LDL-C) levels (130-189 mg/dL) increased.

Antiviral resistance: Resistance against antiretroviral drugs was found in 4/27 of the patients. Three of the patients were ART-naive before and one of them gained ARV resistance during the course of the treatment. Detected gene mutations are given in detail together with the table (Table 1).

Follow up period: The mean follow-up period was 67.1 (6-192) months. Nine-teen (76%) patients received the same regimen during the course of the treatment. Initial ART was changed in six patients due to possible drug side effects (n: 2) and antiviral resistance (n: 4). One of those patients was a 11 year old girl who experienced non-compaction cardiomyopathy and her ART was changed as emtricitabine/tenofovir disoproxil fumarate and dolutegravir sodium to reduce cardiac toxicity.

Discussion

According to evidence from randomized controlled trials and epidemiological data, the ART of choice has consisted the combination of 2 NRTI plus 1 NNRTI or a PI for more than 17 years (5-8). There are several unresolved issues, notably the toxicity associated with NRTI, especially thymidine analogs, and the possibility of cross resistance, which may affect subsequent treatment. The development of new antiretroviral drugs with simpler dosing regimens and lower toxicity has led to evaluation of innovative strategies such as dual therapy for initial ART in treatment-naive patients, with the aim of preventing long-term toxicity and increasing treatment adherence. Despite encouraging results, some combinations have proven unsatisfactory outcomes.

In this study 81.4 % (n= 22/27) of the patients received NRTI and PI-based regimes and 19 patients were taking the same drugs for about 71 months (8-132). In this group frequent episodes of vomiting with no dehydration (n: 2) and elevation of LDL-C levels (n: 2) due LPV/r were detected. Despite these disturbing symptoms we did not change the medication and these complaints have resolved with basic recommendations like regulation of diet habits, over time. Using LPV/r-based regimens caused some metabolic disturbances although these did not yield any serious complications in the long-term. Besides, immunologic and virologic responses were good.

Laboratory tests revealed hyperlipidemia, increased amilase levels and neutropenia. However, none of them required a change in therapy. In our study only one patient (n= 14.3%) who was on AZT therapy became anemic enough to require blood transfusion. There is a risk of anemia among HIV-infected children on ART containing AZT (9). AZT was switched to TDF and the anemia resolved. Renner and colleagues reported that severe anemia was frequent at baseline and guided the first-line ART prescription although its incidence seemed rare among children (10). Severe malnutrition at baseline was a strong predictor for development of severe anemia, therefore clinicians should be aware of basal anemia when starting antiretroviral treatment.

Antiviral drug resistant was observed in 4/27 patients. Two patients had NRTI resistance mutation M184V, conferring resistance to 3TC/ FTC. 3TC was switched to TDF. Another patient with early virologic failure had INT gene and PI gene mutations. Resistance to the integrase inhibitors, raltegravir and elvitegravir, is due to L68V, L74I mutations in the integrase gene (11). We switched to dolutegravir based regime which resulted in virologic response within 6 months.

A patient with treatment history of AZT, 3TC, LPV/r and DRV gained NRTI and PI resistance mutations. But NNRTI mutations A98G and Y181C cannot be related to the reported drug treatment and may either be transmitted from mother to child or may be due to an incomplete anamnestic report before starting the current regimen. High frequency of drug resistance mutations mainly NNRTI-associated, was observed in a nationwide surveillance among newly diagnosed HIV-infected children in Nigeria. Their results support the use of protease inhibitor-based first-line regimens in HIV-infected young children regardless of prevention of mother-to-child transmission history (12). The WHO recommends protease-inhibitor-based first-line regimen in infants due to risk of drug resistance (1).

Due to the rising numbers of children infected with HIV-1 in Turkey, HIV/AIDS might develop into a priority public health concern in the coming years. In summary, we found drug resistant variants in 14.8% (4/27) of the analyzed samples. Three

patients displayed variants presenting resistance mutations resulting from transmission or therapy interruption. Therefore, we believe in our country, routine baseline resistance testing urgently needs to be standardized for children as they are not only at the start of their ART but also at the beginning of their lives, which could be restricted dramatically by the wrong selection of antiretroviral drugs.

Conclusion

Despite small number of patients, our results show that NRTI and PI-based regimes are good option in children for immune recovery.

Ethics Committe Approval: The study was approved by the institutional ethical review board (2017/1290).

Informed Consent: As the study was a retrospective review of the laboratory data, patient consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept - ÖK; Design - SHT; Supervision - SHT, AS, AA; Data Collection and/or Processing - ÖK, MK, MOK; Analysis and/or Interpretation - ÖK, MK, MOK; Literature Review - ÖK, SHT; Writing - ÖK, SHT; Critical Review - SHT, AS, AA.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that they did not receive financial disclosure.

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