Nine-year follow-up of HIV-infected Romanian children and adolescents receiving lopinavir/ritonavir-containing highly active antiretroviral therapy

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Abstract

Introduction Many Romanian children were infected nosocomially with human immunodeficiency virus (HIV) in the late 1980s. The Romanian-American Children's Center of Excellence in Constanța continues to follow approximately 450 of these patients. In 2001, 414 of these patients were initiated on triple therapy including lopinavir/ritonavir. Data from this cohort treated through August 2006 were published in April 2007 demonstrating that the treatment was well tolerated, with 337 children (81%) remaining on therapy after a median duration of >4 years. The current article describes the results of continued analysis of this cohort through end 2010. The objective of the study was to determine the long-term clinical outcomes of children and adolescents commenced on antiretroviral therapy (ART) including lopinavir/ritonavir.

Methods Data were extracted retrospectively from the charts of the 336 patients remaining on lopinavir/ritonavir in August 2006. The following outcomes were analyzed: mortality, current patient status, viral load (VL), CD4 counts and reasons for discontinuation of lopinavir/ritonavir.

Results The median age at initiation of lopinavir/ritonavir was 14.0 years (range 5.4 to 20.0 years). The median time on lopinavir/ritonavir treatment was 7.5 years (interquartile range 5.7 to 8.6 years). Overall mortality was 13.5%. Of the original 414 patients started on lopinavir/ritonavir in 2001, 199 (48.1%) remained on this therapy at the end of 2010 and of these 63.8% had undetectable viral load.

Conclusion Despite initial suboptimal ART, a significant proportion of patients subsequently treated with a lopinavir/ritonavir based regimen remained on this therapy for up to nine years.

Keywords HIV/AIDS, antiretroviral therapy, lopinavir/ritonavir.

Introduction

The Romanian-American Children's Center of Excellence in Constanța has been operational since April 2001.¹ It represents a unique

partnership arrangement between the Baylor College of Medicine International Pediatric AIDS Initiative (BIPAI) and the government of Romania, providing medical care, including

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antiretroviral treatment, and psychosocial services for HIV-infected children and adolescents. Many thousands of Romanian children were infected horizontally with HIV in the late 1980s probably through the transfusion of whole human blood unscreened for HIV and the reuse of disposable needles. The Romanian-American Children's Center of Excellence in Constanța continues to follow approximately 450 of these patients. In 2001, 414 of these patients were initiated on triple therapy including lopinavir/ritonavir.

Data from this cohort treated through August 2006 have previously been published in Pediatrics in April 2007.² The results of the original analysis demonstrated that the treatment was well tolerated, with 337 children (81%) remaining on therapy after a median duration of >4 years in August 2006. Thirty-seven deaths occurred during this period.

Lopinavir/ritonavir-containing highly active ART has been recommended for initial therapy of HIV infection in children by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children of the US Health Resources and Services Administration and National Institutes of Health.³ Approval of the drug for children was based largely on the results of a 48-week study of its safety and efficacy in 100 HIV-infected children 6 months to 12 years of age.⁴ One other study has been published with data from 116 children treated with lopinavir/ritonavir for up to 164 weeks.⁵ There are few other studies published regarding the long-term safety and effectiveness of lopinavir/ritonavir-containing ART in large cohorts of HIV-infected children and adolescents. The program of child and adolescent ART was initiated at the Romanian-American Children's Center of Excellence in November 2001. This article describes the updated clinical outcomes of the previously reported results of the 414 HIV-infected Romanian children commenced on ART with lopinavir/ritonavir.¹

Methods

Patient care

This is a retrospective chart review study and an update on the clinical outcomes of a group of patients commenced on ART with

lopinavir/ritonavir, that have been previously reported. Full details of patient care are to be found in the earlier publication.¹ In addition to triple antiretroviral therapy, patients received prophylaxis for *Pneumocystis jiroveci* pneumonia according to established guidelines;⁶ nutritional support and antibiotic therapy were prescribed as needed.

All of the patients and caregivers were counseled initially and monthly regarding the importance of medication adherence. Home visits permitted monitoring of antiretroviral medication storage, administration and adherence, and factors in the home and family that might impact treatment.

All of the treated children and adolescents were evaluated clinically on a monthly basis and had routine laboratory tests on a three to six monthly basis. However, because of cost considerations, plasma HIV-RNA measurements (Roche Molecular Systems, Branchburg, NJ) were performed only on a subset of treated children and adolescents until 2005, when the test became available more routinely. In general, CD4 lymphocyte counts were obtained at baseline and at intervals of approximately 6 to 12 months.

Analytical methodology

The data were extracted from the clinic's electronic medical record or from patient charts. All data collected in the normal medical care of the original cohort of 414 patients were taken into consideration. Unfortunately the records of one patient were missing, explaining the difference between 337 patients on therapy at the end of the previously reported analysis and the 336 on therapy at the beginning of the current analysis.¹ The following specific data were captured: baseline and demographic information, latest documented patient status, latest documented viral load (VL) and VL profile over time since initiation of lopinavir/ritonavir, baseline and latest CD4 count and CD4 profile over time since initiation of lopinavir/ritonavir, causes of death, reasons for discontinuation of lopinavir/ritonavir and adverse events associated with lopinavir/ritonavir resulting in discontinuation. The data was analyzed using

STATA 12.1 Special Edition software (StataCorp: 2011, College Station, TX, USA).

The primary outcome was to determine the long-term mortality of children and adolescents commenced on ART including lopinavir/ritonavir. Long-term mortality was reported using incidence density where the number of deaths was divided by the number of patient-years accumulated during the study period. The study period began on the date of lopinavir-ritonavir initiation and ended on 31 December 2010. Patient-years was calculated using 1st August 2006 up until either the date of the patient's last visit, the date of the patient's death or the end of the study period.

Additional analyses were conducted and reported. The mean age at initiation of lopinavir-ritonavir and the median time on lopinavir/ritonavir were calculated. A determination of the percentage of patients still alive whose VL was undetectable according to the latest documented measurement was assessed. The proportion of living patients with VL <400 copies/mL was reported. The change in CD4 count in patients still alive between baseline (as measured in 2001) and the latest documented measurement was reported. Patients with a missing baseline CD4 value were omitted from the change in CD4 analysis.

A determination of the current status of the original cohort of patients commenced on ART including lopinavir/ritonavir was assessed. For this, patients were classified as alive and on lopinavir/ritonavir, alive but discontinued from lopinavir/ritonavir, died, lost to follow-up or transferred out from care at the study site clinic. The specific reasons for discontinuation of lopinavir/ritonavir were tabulated into one of the following designations: death, adverse event, laboratory abnormality, HIV disease progression or documented treatment failure, non-adherence to ART, lost to follow-up, patient discontinued of own accord or at parents' wish and transferred out from care. In addition, the causes of death and specific adverse events resulting in discontinuation were defined.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and was consistent with

Good Clinical Practice (GCP) and applicable regulatory requirements. All personnel involved in conducting this study were qualified by education, training, and experience to perform their respective tasks. The protocol and data collection tools were first submitted for approval to the relevant local IRB (Institutional Review Board) in Romania and subsequently to the Baylor College of Medicine IRB in Houston, Texas. For the purposes of analysis and presentation, all data were de-identified.

Results

Baseline data

The original study population of 414 children commenced on lopinavir/ritonavir containing ART in 2001 consisted of adolescents, the majority of whom had advanced HIV disease and had been infected with HIV in 1988 to 1989. The mean age was 14 years (range 5 to 18 years), 222 (54%) male and 192 (46%) female. The distribution by Centers for Disease Control and Prevention (CDC) clinical category was A: 8 (2%), category B: 320 (77%) and category C: 86 (21%). Among 299 of the children for whom CD4+ lymphocyte count was available, the mean baseline value was 292 cells/ μ L (range: 1-1433). Only 97 children had plasma HIV-RNA concentrations measured immediately before initiation of lopinavir/ritonavir-containing ART, the mean baseline measure being 152,036 copies/mL (range: <400 – 930,000). Most patients had been pre-treated with mono-therapy, dual therapy or triple therapy depending on the timing of initiation of ART. Among 340 (82%) ART experienced patients, 126 had previously received only nucleoside reverse transcriptase inhibitors (NRTIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs), while 214 had received protease inhibitors. Information concerning prior ART was not available for 39 patients and 35 were treatment-naïve. During the study, in the event of discontinuation of lopinavir/ritonavir because of treatment failure or adverse events, a large range of antiretroviral drugs have been utilized in this population, including other protease inhibitors, efavirenz and more recently raltegravir and enfuvirtide.

The current analysis involved extension of the duration of therapy on lopinavir/ritonavir through the end of 2010. It included 336 patients. The age of starting lopinavir/ritonavir of these 336 patients was similar to the original cohort, mean 14.1 years, range 5.4 to 20.0 years. The median time on lopinavir/ritonavir through the conclusion of 2010 was 7.5 years (interquartile range 5.7 to 8.6 years).

Mortality

Upon review of the medical charts, 15 patients included in the original analysis of the 414 children commencing ART were not included in the mortality calculations since they were no longer actively in care in August 2006 at the study site clinic. These patients were classified as follows: died (7), lost to follow-up (7) and transferred care to another clinic (1) before the beginning of the study period. A total of 56 of the original cohort of 414 patients died (13.5%). Between August 2006 and the end of 2010, 19 of 321 patients died, (5.9%; 1.5 deaths per 100 patient-years). In 41.1% of cases (23 patients) the exact cause of death was not known (the death certificates indicating cardiorespiratory arrest in most of these cases). The following exact causes were recorded for the remaining 33 patients: tuberculosis (14 cases), encephalopathy (7 cases), cytomegalovirus (3 cases) and pneumonia (7 cases), allergic reaction to anesthesia (1 case), hepatic carcinoma (1 case).

Virologic and immunologic outcomes

VL measurements within 6 months of analysis were obtained for the 199 patients remaining on lopinavir/ritonavir at the end of 2010. Of these, 63.8% had undetectable levels, the median VL being <400 copies/mL (range <400 to 845,000).

CD4 counts within 6 months of analysis were obtained for all 199 patients remaining on lopinavir/ritonavir at the end of 2010, the mean being 629 cells/ μ L, (standard deviation = 383 cells/ μ L) as illustrated in Figure 1. Of these 199 patients, 154 had baseline CD4 counts prior to

commencing lopinavir/ritonavir in 2001. The mean change in CD4 count for these patients between November 2001 and the end of 2010 was plus 278 cells/ μ L (standard deviation = 442 cells/ μ L).

Figure 1: Histogram of most recent CD4 for patients still on lopinavir/ritonavir on 31st December 2010

End of study patient status

Taking the entire population of 414 patients together, 215 patients were permanently discontinued from therapy by the end of 2010. Figure 2 is a flow chart illustrating the disposition of patients from November 2001 through the end of December 2010 at which time 199 patients (48.1%) remained on lopinavir/ritonavir. Treatment failure was for the most part judged purely on clinical grounds, because resistance genotyping was not readily available. For this reason it was also difficult to differentiate clearly between treatment failure and non-adherence and, therefore, these categories have been combined in Figure 2.

Among the 105 patients discontinued because of non-adherence or treatment failure, resistance genotyping was performed on 70, of whom 25 were shown to have clear or partial resistance to lopinavir/ritonavir.

Short-term interruptions of therapy were relatively common, occurring in 154 patients

because of adverse events, patients' decision or temporary unavailability of antiretroviral therapy. The adverse events leading to discontinuation were intractable vomiting (11), lipodystrophy (5), hepatitis (3) gastrointestinal side effect (1) and unknown (1).

Figure 2. Flow chart of patient disposition

Discussion

This analysis has demonstrated the long-term use of lopinavir/ritonavir in combination with a variety of other antiretroviral drugs in a population of patients who began therapy as children or young adolescents. To the authors' knowledge this is the longest reported follow up of such patients on this therapy. These results compare favorably with rates of failure on protease inhibitors in adults reported in the

literature.^{7,8,9} In the study which lead to approval of lopinavir/ritonavir for children, 21% of the population had already experienced virologic failure by 48 weeks of therapy.⁴

It is important to point out that this population posed several serious challenges with regard to achieving good clinical outcomes. The majority of patients had received sub-optimal antiretroviral therapy prior to initiating lopinavir/ritonavir. Most had been treated with variable periods of either mono-therapy or dual therapy. In addition the population had high levels of social deprivation, had suffered from widespread discrimination and stigma and struggled to cope with the known problems of adolescents with regard to maintaining good adherence to therapy.^{10,11}

The most common reasons for discontinuation were treatment failure or non-adherence to ART (105 cases), while only 21 patients were discontinued because of adverse events. Also, 127 of 199 patients still on lopinavir/ritonavir treatment at the end of the study period had undetectable VL. Overall this is further testament to the long-term usage of lopinavir/ritonavir in this population. The 72 patients with detectable VL were continued on therapy because they were considered to be deriving significant benefit on the basis of clinical and immunologic grounds, phenomenon which has been previously reported in the literature.^{12,13}

Conclusions

This analysis provides the longest duration of follow-up, reported to date, of lopinavir/ritonavir in a population of HIV-positive children, adolescents and young adults in Romania. This study demonstrated that a large proportion of the original cohort of children and adolescents commenced on ART including lopinavir/ritonavir in 2001 remained on such therapy with their underlying HIV disease well controlled through the end of 2010.

Conflicts of interest All authors – none to declare.

Author contribution: All authors contributed significantly to the manuscript. RSBW: principal author; SR: principal investigator; SiR: co-investigator; IMD: co-investigator; RCC: co-investigator; HLS: manuscript

reviewer; NRC: manuscript reviewer; GES: manuscript reviewer; AMS: manuscript reviewer; HRD: statistician; MWK: manuscript reviewer.

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