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Effect of First Line Therapy Including Efavirenz and Two Nucleoside Reverse Transcriptase Inhibitors in HIV-infected Children

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Abstract
Objective: In an intent-to-treat study, reduction of viral load, increase in CD4 cell count, clinical benefit and adverse reactions were examined in HIV-infected children receiving first line therapy including efavirenz.
Methods: The data of 10 perinatally infected children (median age: 5.8 years) were evaluated during a treatment period of 24 months. Viral load and CD4 cell count were measured every 4 – 8 weeks. Pharmacokinetic evaluations of evafirenz were performed in all patients at study onset. Adverse reactions were reported after obtaining interval history and examination.
Results: At base line, median CD4 cell count was 378 cells/µl (21%) and median viral load was 350 000 copies/ml (5.5 log10 copies/ml).

After 24 months of treatment, the median viral load reduction was > 3.5 log10 copies/ ml and HIV-1 RNA < 50 copies/ml was found in 8/10 children (80%). Median CD4 cell count increased to 721 cells/µl (24%) after 3 months and was maintained at a level of >1000 cells/µl (> 25%) after 24 months of treatment. Regarding efavirenz levels, C min. values ranged from 845 to 3550 ng/ml (median: 1845 ng/ml) and C max. values from 2380 to 24 200 ng/ ml (median: 3670 ng/ml). The most common adverse effect was a mild skin rash (4/10 children). CNS symptoms were recorded in one patient and no hyperlipidaemia was seen.
Conclusion: First line therapy with efavirenz and two NRTIs was well tolerated by HIV-1 infected children and the reduction of viral load seems to be similar to single protease inhibitor-containing regimens.

Key words: efavirenz, first line therapy, viral load, plasma level, HIV, children

Introduction

The guidelines for the use of antiretroviral agents in paediatric HIV infection strongly recommend two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a protease inhibitor or the combination of two NRTIs plus the non-nucleoside reverse-transcriptase inhibitor (NNRTI) efavirenz as initial therapy [1]. This recommendation is based on clinical trials in previously untreated adult patients und pre-treated paediatric patients [2, 3]. A large, randomised, multi-national study has been started which compares NNRTI- with PI-containing initial therapies in HIV infected children (PENPACT 1, PACTG 390).

Until now, a sustained reduction of viral load has been demonstrated with a triple therapy including two NRTIs and a protease inhibitor in previously untreated HIV- infected children [4, 5]. Although this regimen was well tolerated, hyperlipidaemia occurred in about 50% of the treated children [4, 6]. NNRTI-containing regimens showed a comparable benefit but less adverse effects than protease inhibitor-containing regimens [2].

Starr et al. investigated the benefit of a combination with a protease inhibitor (nelfinavir), a non-nucleoside reverse-transcriptase inhibitor (efavirenz) and two NRTIs in HIV-infected children previously treated with NRTIs [3]. After 48 weeks, 76% of these children had plasma HIV-1 RNA levels < 400 copies/ ml and 63% had levels of < 50 copies/ ml. In a recent study, Starr et al. (2002) investigated the effect of an antiretroviral regime containing a liquid efavirenz formula and nelfinavir in children mostly pre-treated with NRTIs [7]. After 48 weeks of therapy, 58% of these children had a viral load below the limit of detection (<50 copies/ml).

Until now there is limited experience with children on first line NNRTI- therapy [8, 9]. The percentage of children with a sufficient viral suppression varied between 60% and 30% and depended on the antiretroviral regime and nevirapine dose.

Results of clinical trials comparing the virologic and immunologic response of evafirenz and nevirapine are controversial [10, 11], some studies showing more virologic failures with nevirapine and others showing equivalent efficacy of the two drugs.

Because no comparative trials of nevirapine and efavirenz have been conducted in children, US - Guidelines do not recommend nevirapine as a first line drug in children older than 3 years.

Efavirenz has good oral bioavailability, a long terminal half-life and is therefore amenable to single daily dosing [10, 12]. Furthermore, efavirenz-containing

regimens are well tolerated and seem to have good antiretroviral potency. Therefore, we tested a combination of efavirenz and two NRTIs in previously untreated children in order to evaluate benefit, adverse effects and compliance.

Patients and Methods

Patients

Ten perinatally HIV-infected children (eight females and two males) were investigated in an open prospective study over a period of 24 months. Study design was approved by the local Ethics Committee.

None of the children had prior antiretroviral treatment. According to North American and German paediatric guidelines [1, 13], antiretroviral therapy was started when patients entered category B or 2. Age of the children ranged between 3.1 and 8.0 years (median: 5.8 years) at study onset. None of the patients had elevated serum levels of total cholesterol, triglycerides or liver enzymes at the beginning of the study.

All patients received an antiretroviral combination of efavirenz and two NRTIs as described in Table 1. For all NRTIs, recommended dosages were used according to the manufacturers and to international HIV treatment guidelines. Initial daily doses of efavirenz ranged between 375 and 480 mg/m^2 (12.5 and 17.0 mg/kg bodyweight) according to the manufacturers recommendations and to the available capsule size.

Baseline Characteristics

According to the paediatric CDC classification [14], four children were in category A2, two patients in category B1, three patients in category B2 or B3 and one patient in category C3 (Table 1). Symptoms of the five B category patients included severe bacterial infections, recurrent diarrhoea, persistent oral mycosis, persistent thrombocytopenia and severe herpes zoster infection. Oesophageal candidiasis and also a severe wasting syndrome were AIDS- determining symptoms in the category C patient.

Before treatment was initiated, CD4 cell counts ranged from 58 to 1376 cells/µl (median: 378 cells/µl) and the percentage of CD4 cells varied from 7.5% to 40%. Initial plasma HIV-1 RNA levels of all patients were in the range of 4.11 – 6.54 log copies/ ml (13 000 – 3 500 000 copies/ml) and the median viral load was 5.5 log (350 000 copies/ ml).

Surrogate Markers

Viral load was measured by the Amplicor test (version 1.5; Hoffman LaRoche, Grenzach Whylen, Germany) and expressed in HIV-1 RNA copies/ml plasma (limit of detection: 50 copies/ml). CD4 cell count was measured by flow cytometry (monoclonal antibodies from Becton-Dickinson, Heidelberg, Germany), expressed in cells/µl plasma. To record therapy-related adverse events, SGOT, SGPT, lipase, triglycerides and cholesterol were monitored. All blood values were monitored every 4 – 8 weeks during the first 3 months of treatment and then followed up every 12 weeks.

Table 1. Baseline characteristics of 10 HIV- infected children at onset of treatment

Characteristic	**Value**
Sex – no.	
Female	8
Male	2
Age	
- yr	
Mean	4.9
Median	5.8
Range	3.1 – 8.0
Weight – kg	
Mean	19.1
Median	17.8
Range	15 - 26
CD4 cell count – per mm^3	
Mean	580
Median	378
Range	58 - 1376
CD4 cell count – %	
Mean	22
Median	21
Range	7.4 - 40
Plasma HIV- 1 RNA level	
– log copies/ ml	
Mean	5.29
Median	5.5
Range	4.11 – 6.54
Category (CDC) – no	
A2	4
B1	2
B2	1
B3	2
C3	1
Antiretroviral therapy:	
Efavirenz plus – no.	
Abacavir + Lamivudine	3
Zidovudine + Lamivudine	4
Didanosine + Stavudine	3

Plasma Efavirenz Levels

Quantification of efavirenz in plasma was carried out by high-performance liquid chromatography (Prof. M. Kurowski, Berlin, Germany). Evaluation was performed according to described methods [15, 16]. As shown by Marzolini et al. in adult patients on once-daily dosing, optimal plasma efavirenz levels ranged from 1000 to 4000 µg/l [12]. Virologic failure has been observed in 50% of reported patients with efavirenz levels below 1000 µg/l and CNS toxicity was approximately three times more frequent in patients with efavirenz levels > 4000 µg/l. Therefore pharmacokinetic evaluations of evafirenz were performed in all patients at study onset after achieving steady state. We measured plasma levels 0h, 1h, 2h, 4h, 8h and 12h or 24h after administration of daily efavirenz doses. In

the case of minimal plasma levels (Cmin) <1000 ng/ml or maximal plasma levels (Cmax) >4000 ng/ml, the efavirenz dose was adjusted accordingly and measurements of plasma levels were repeated.

Determination of Genotypic Resistance

Viral RNA isolation and generation of sequence data for the Reverse Transcriptase (RT) and Protease (PR) gene regions were performed as described elsewhere [17, 18]. Only known mutations conferring resistance to NRTI and NNRTI were considered, including changes at positions 65, 74, 98, 100, 103, 106, 108, 181, 184, 188, 190, 225, and 236 of the RT gene. Thymidine analog resistance mutations (TAM) were defined as the mutations M41L, D67N, K70R, L210W, T215Y/F, and K219E.

Statistics

No child stopped therapy because of adverse effects or loss of virological control within the 24 months of follow-up. Therefore, data were evaluated by an intent-to-treat analysis. Comparison between surrogate markers was made with the Wilcoxon signed rank test. HIV-1 RNA copies and CD4 cell count before onset and after 3, 6, 12 and 24 months of treatment were evaluated and compared.

Results

Clinical Benefit

Severe bacterial infections, recurrent diarrhoea, herpes zoster infection or manifestation of opportunistic infection such as *Pneumocystis carinii* pneumonia were not seen in category B and C patients during the 24 months of treatment. Symptoms of oral mycosis and an initial thrombocytopenia improved in the first weeks of treatment and then disappeared. The category C patient recovered slowly from oesophageal candidiasis and gained weight. No patient on treatment had signs of disease progression.

Viral Load

Median viral load decreased significantly from 5.5 log10 copies/ml (median: 350 000 copies/ ml, range: 13 000 - 3 500 000 copies/ml) to 2.2 log10 (median: 160 copies/ml) after 3 months of treatment. From month 6 to the end of the study period, median viral load was maintained below 2.0 log10 (median: < 50 copies/ml). After 6 months of treatment, a median viral reduction of > 3.5 log10 copies/ml was attained (Table 2). The decrease in viral load was statistically significant (global P value: < 0.01), comparing initial values and values after 6, 12 and 24 months.

HIV-1 RNA levels below the limit of detection were found in 4/10 patients after 3 months of treatment and in 8 patients after 6 months. At the end of the treatment period (2 years), 8/10 patients maintained a viral load below the limit of detection (Table 2). 2/10 patients had repeatedly HIV-1 RNA values between 80 and 3000 copies/ml (1.9 – 3.3 log10 copies/ml).

CD4 Cell Count

Median CD4 cell count increased significantly from 378 cells/µl (median: 21%) at study onset to 721 cells/µl (median: 24%) after 3 months of treatment. After 12 and 24 months, the CD4 cell count had increased to a median of 981 cells/ µl and 1220 cells/µl respectively, and the percentage of CD4 cells stabilised in all patients at values > 25% (Table 3). The increase in median percentage and number of CD4 cells was statistically significant (global P value: 0.01) at 6, 12 and 24 months.

Table 2. Viral load (VL) values during 24 months of treatment.

Treatment - months	HIV-1 RNA copies – log10 median	HIV-1 RNA copies – log10 range	HIV-1 RNA < 50 copies/ ml patients	Reduction of VL – log10 median
- 1	5.5	4.1 – 6.5	0 / 10	
+ 3	2.2	< 1.7 – 3.1	4 / 10	3.2
+ 6	< 1.7	< 1.7 – 3.3	8 / 10	> 3.5
+ 12	< 1.7	< 1.7 – 2.2	9 / 10	> 3.5
+ 24	< 1.7	< 1.7 – 3.1	8 / 10	> 3.5

Table 3. CD4 cell count during 24 months of treatment.

Treatment – months	CD4 cell count - cells / µl median	CD4 cell count – cells / µl range	CD4 cell count – % median	CD4 cell count – % range
-1	378	58 - 1376	21	7 - 47
+3	721	83 - 2404	24	10 - 35
+6	828	267 - 2272	31	15 - 36
+12	981	471 - 2347	33	26 - 45
+24	1220	487 - 1747	38	27 - 49

Table 4. Pharmacokinetic evaluations of evafirenz in 10 patients at study onset.

Parameter	Mean	Median	Range
C min. (ng/ ml)	1737	1845	845 – 3550
C max. (ng/ ml)	4429	3670	2380 - 24 200
T max. (hours)	2.23	2.24	0.68 – 4.33

Plasma Efavirenz Levels

As shown in Table 4, C min. values ranged from 845 to 3550 ng/ml (median: 1845 ng/ml). Two patients had trough levels < 1000 ng/ml (845 and 861 ng/ml) and the trough levels of a further two patients were barely above 1000 ng/ml (1070 and 1100 ng/ml). Maximal levels ranged from 2380 ng/ml to 24200 ng/ml (median: 3670 ng/ml). C max. levels > 4000 ng/ml were seen in four patients (8011, 8920, 9670 and 24 200 ng/ml). Median time to reach maximum plasma concentration (T max.) was 2.24 hours (range: 0.68 – 4.33 hours).

3 of 4 patients with minimal plasma levels below and barely above 1000 ng/ml received a daily efavirenz dose of < 13.5 mg/kg bodyweight whereas patients with daily efavirenz doses of > 14 mg/kg bodyweight had sufficient C min. values (> 1500 ng/ml). Two patients with maximal levels above 9000 ng/ml received a daily efavirenz dose of > 16.5 mg/kg bodyweight. After adaptation of dosage, these patients had plasma efavirenz levels within the reference ranges. In one patient, re-evaluation of trough levels showed persistent low C min. values (< 1000 ng/ml), suggesting non-adherence.

Adverse Reactions

In general, triple therapy with efavirenz and two NRTI was well tolerated. All adverse events occurred during the initial phase of treatment. The most common side-effect was a transient rash of moderate severity (4/10 patients). None of these children had febrile episodes at the time of the rash. In one patient each, transient symptoms of diarrhoea, arthralgia or lack of concentration were noted.

One patient reported CNS symptoms such as abnormal dreams and symptoms of depression during the first 6 weeks of treatment. Dosage was reduced after pharmacokinetic evaluation revealed a high peak plasma efavirenz level (24 200 ng/ml).

No case of persisting elevation of serum triglycerides, cholesterol or liver enzymes or signs of peripheral lipodystrophy occurred during the 2 years of treatment.

Genotypic Resistance

Genotypic resistance assays were performed in 2 of 10 patients, who had repeatedly HIV-1 RNA values >50 copies/ (80 to 3000 copies/ml).

In both patients the K103N and V108I mutations were found corresponding with phenotypic resistance to NNRTI. The patient with a permanent viral load > 1000 copies/ ml also had the M184V mutation, indicating lamivudine resistance.

Discussion

Our data show a lasting and profound antiretroviral effect of an efavirenz-containing triple therapy in most of the therapy-naïve HIV-infected patients studied. Median reduction of viral load was > 3.5 log10 and 8/10 patients had viral loads below the limit of detection (<50 copies/ml) after 24 months of treatment. These results are confirmed by clinical studies in adult patients on an antiretroviral combination including efavirenz [2].

About 60% of paediatric patients pre-treated with NRTIs and PI had a reduction of viral HIV-1 RNA load of <50 copies/ml after 48 weeks of antiretroviral treatment with NRTI, nelfinavir and efavirenz [3, 7]. Engelhorn et al. found a viral load reduction to below the detection limit in 9/15 (60%) heavily pre-treated children after 52 weeks of combination therapy including efavirenz [20]. 70% of partly NRTIs-experienced adult patients on triple therapy with NRTIs and efavirenz had suppression of HIV-1 RNA to undetectable levels [2].

Looking at NRTIs- and single protease inhibitor-containing regimens, a smaller percentage of paediatric patients with HIV-1 RNA < 50 copies/ml was found. 48 % of therapy-naïve paediatric patients of the PENTA 5 study on treatment with the protease inhibitor nelfinavir had undetectable viral loads after 48 weeks of treatment [5]. In our preliminary study we saw a reduction of viral load to below the limit of detection in 44% (7/16) of previously untreated children on a nelfinavir-containing triple therapy over a period of 12 months [4].

Because of the small number of paediatric patients, comparison between NNRTI- and protease inhibitor-containing regimes remains difficult. Nevertheless, the antiretroviral effect observed in children on an efavirenz- and NRTI- containing regimen seems to be similar to that reported with other regimes containing NRTIs and a single protease inhibitor.

CD4 cell count increased in category 3 and 2 patients above 25% and was maintained at this level in all treated patients after 12 and 24 months of treatment. Thus immunological reconstitution could be achieved, especially in three patients of category 3. No patient on treatment had signs of disease progression and no opportunistic infections occurred. Therefore, the effect of efavirenz on the immune system of our studied patients is comparable to that in therapy-naïve children on other antiretroviral regimes [4, 5].

Quantification of plasma efavirenz levels revealed good adherence in at least nine of ten patients. Low trough levels in four patients and a high peak level in two further patients required adaptation of dosage. Our data indicate that efavirenz could easily over- or

underdose in paediatric patients. To maintain sufficient plasma levels, the daily efavirenz dose should not fall below 13.5 mg/kg bodyweight and to avoid adverse (CNS) effects, efavirenz doses should not go beyond 16.5 mg/kg bodyweight. Furthermore, we found a large range of plasma levels (C min. and C max. values) in our patients who receive the recommended dosage of efavirenz. Therefore, like others [12, 21] we recommend drug monitoring in all paediatric patients at the onset of efavirenz therapy in order to avoid virologic failure as well as CNS toxicity.

Observed adverse effects of efavirenz seem to be transient and in part dose- related. Transient rash, symptoms of diarrhoea, arthralgia or lack of concentration were reported, but no patient discontinued treatment. As mentioned above, the only severe effect was a case of CNS toxicity which occurred in one child over a period of 6 weeks. A dose- related effect was most probable, as described by others [12].

In contrast to patients on protease inhibitor- containing regimes, no persistent hypertriglyceridaemia or peripheral lipodystrophy was seen in our patients.

Lack of hyperglycaemia and dyslipidaemia is an advantage of NRTIs- and NNRTI– containing regimes. The single daily administration is an additional advantage, particularly for the treatment of paediatric patients. On the other hand, a rapid emergence of resistant HIV variants in patients with an incomplete viral suppression could be a great risk of efavirenz-containing regimes. K103N and V108I mutations were found in two of our patient with repeatedly HIV-1 RNA values > 50 copies/ml. These mutations and the Y188L/C mutation lead to cross-resistance to all presently available NNRTIs (efavirenz, nevirapine and delavirdine), as also shown in other patients with treatment failure [22, 23]. Until now, the emergence of cross-resistance in patients receiving protease inhibitor- versus patients receiving NNRTI- regimes has not been compared in paediatric clinical trials.

Particularly for children, an easy to manage and well tolerated therapeutic regimen is of great importance in achieving good adherence. Simple drug monitoring is of additional importance in order to individualize the treatment. These conditions are well met by efavirenz-containing regimens.

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