Case Report

Clinical and biological outcomes in an HIV-positive child treated with the immuno-modulator 6,6’-dithiodinicotinic acid (CPDS) over four years: A case report

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The elimination of HIV-AIDS by 2030 is a challenging target for a country such as the D.R. Congo, since currently fewer than 50% of persons living with HIV (PLWH) are under antiretroviral treatment (ART) and have a viral suppression. There also a high rate of death of PLWH in D.R. Congo. Accessible, affordable and sustainable immunotherapy, coupled with ART, can provide a substantial support to eliminating HIV. The purpose of this paper is to describe the measured clinical and biological profiles over a 4-year period of treatment with the immunomodulator 6,6’-dithiodinicotinic acid (CPDS), of a patient who was only 10-months old at the start of treatment. The patient was part of a larger two-year clinical trial of CPDS on HIV-AIDS. This study found that despite his advanced clinical HIV stage (being born to parents with terminal HIV), the patient maintained his weight and lymphocyte counts, and did not experienced any severe HIV-AIDS-related illness during the study period. This suggests a beneficial or protective effect of CPDS treatment. The patient shifted to ARV at 5-years old and is now 17-years old, and under first-line ART. The study concludes that survival of this child could likely be attributed to CPDS. We therefore recommend exploring further the simultaneous use of ART and CPDS immunotherapy for a greater clinical and biological benefit of PLWH. We also recommend further study into the mechanism of action of the compound.

Key words: HIV-AIDS treatment, immunomodulation, 6,6’-dithiodinicotinic acid.

INTRODUCTION

The clinical management of HIV/AIDS by standard antiretroviral therapy (ART) using the combination of antiretroviral (ARV) drugs alone cannot eradicate HIV reservoirs (Williams et al., 2011; Zhang and Crumpacker, 2013; Harrer et al., 1996). The interest of immunotherapy in HIV treatment is theoretically well established
In this case report, the focus is on one of the 34 participants, given the particular fact that he was only 10 months old at the beginning of the trial, in 2002 (Ndarabu et al., 2017). He continued to take CPDS alone for 2 years after the completion of the trial before he shifted to ARV treatment at age 5 (a total of 4 years under CPDS-only treatment). He is now 17-years old and regularly followed at Monkole Hospital under ART. The objective of this case report is to highlight the clinical and biological profile of this participant over the 4-year period under CPDS treatment. The clinical parameters considered are: weight, illness episodes or occurrence; the main biological parameter consists of lymphocytic counts (Grassetti and Moro, 2013).

CASE REPORT

The patient was born in December 2001 to HIV positive parents. He was initially admitted at Monkole Hospital in Kinshasa, D.R. Congo at 10-months of age, in October 2002. At that time he was at Stage 2 per the World Health Organization (WHO) Clinical Staging of 1990 criteria, and Stage B2 per the US Centers for Disease Control and Prevention (CDC) pediatrics HIV classification (WHO, 1990; CDC, 1994). There were no medical details about circumstances of birth or the past medical history of the mother and the child. The patient’s birth weight was unknown. He was the sixth out of seven siblings. The last-born was premature and died at 6 days after birth. The father died few months later from HIV-AIDS. The mother was previously followed for HIV-AIDS in another medical facility in Kinshasa, without ART. At that time, access to ARV was not universal and required a significant expense that the mother could not afford. The Prevention of Mother to Child Transmission of HIV (PMTCT) policy then in force advocated only a single-dose of Nevirapine (NVP) for the exposed newborn and NVP single-dose/Tritherapy, depending on the mother’s eligibility to receive ART (CD4 < 350/µl or WHO clinical stage ≥ 3). Breastfeeding was the rule. When the mother was 36-years old, she started her medical visits at Monkolé Hospital (in September, 2002). She was at stage 4 of WHO HIV clinical staging (WHO, 1990), with a severe wasting syndrome, weighing only 38 Kg and displaying low values for counts of lymphocytes; CD4 at 145/µl, CD8 at 392/µl and CD4/CD8 at 0.37. This advanced clinical stage resulted in her death 7 months later, in April 2003. The patient was enrolled in the study following the settled inclusion criteria reported in the previous study with the approval of the Ethical Committee, assigned reference N/Réf: 002/CEFA-MONKOLE/CE/2002 as noted in (Ndarabu et al., 2017), and also with the consent of parents and the research team, considering the expected benefit of the intervention respect to any potential risk which in this case was very unlikely. At the beginning of the treatment, the clinical and biological parameters of the patient were as follows: 8 Kg of body weight at 10-months old, T° 36.8°C, WBC 11,500 mm3 (N27L69E2M2), HCT 21%. Lymphocytes count (absolute number/µl): CD4 787; CD3 3021; CD8 >2000; CD4/CD8: 0.39. Viral load was not available. The immunomodulator used was CPDS (12 mg/Kg oral capsule twice a day).

Description of clinical and biological parameters

The patient’s clinical and biological parameters of weight, ailment episodes, psychomotor development, CD4 count, and clinical evolution were monitored as part of this study. The results are summarized below.

Weight

As per the specified parameters in well-recognized tables for growth (Figure 1) from the World Health Organization (WHO) using the Z-scores of weight-for-age for boys from birth to 5-years old, we recorded the weight of the patient at different medical visits. The weight curve from the
Ailment episodes

Table 1 shows the different clinical visits of the patient under CPDS treatment, along with the illnesses identified and biological findings. Leukocyte count is in absolute number. The relevant illnesses were made of bronchopneumonia (Figure 2), rhinitis, enteritis, prurigo and shingles. No AIDS-related ailments were noted.

Psychomotor development

The child was awake according to his age throughout CPDS intake. The evidence for spoken language occurred around 12 months of age with a slight stuttering. Walking also occurred at this time.

CD4 count

Numbers of CD4, CD3 and CD8 lymphocytes are expressed by microliter on Table 1. With respect to lymphocytic count, CD4 values remained at a mild (moderate) suppression level at less than 12 months of age, and also from 12 months up to 5-years old, suggesting the maintenance of immune system function under CPDS treatment.

Clinical evolution and comments

The death of the patient’s father and mother from HIV-AIDS-related symptoms occurred when he was 13 and 16-months old, respectively, suggesting that they had been already in advanced stages of AIDS at the time he was born. This suggests the possibility that he was potentially infected in utero. At 10 months of age, when we started following the patient, the hospital did not have access to a biomolecular tool for HIV testing, and the diagnosis of HIV was made according to the National Policy in force (Minister of Health DRC, 2004), using an algorithm combining the risk factor (HIV exposed infant), the clinical pattern (small for age) and antibody testing (positive Elisa testing). The diagnosis was later confirmed at 18-months old with the concordance of three positive rapid test of HIV: Determine™, Double-Check™and Unigold™. In this context, we could therefore not definitively establish whether the maternal-to-child transmission of HIV occurred between the pre-, peri- or post-natal period.

DISCUSSION

As the patient was at stage B2 of CDC pediatric HIV classification at baseline, this suggests a certain level of
Table 1. Clinical events and biological data during a 4-year follow up period.

<table>
<thead>
<tr>
<th>Date</th>
<th>Diagnostic Indicator</th>
<th>Lymphocyte count</th>
<th>Blood cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/10/2002</td>
<td>Small size for his age</td>
<td>CD4 787 CD3 3,021 CD8 &gt; 2,000</td>
<td>HCT 29% WBC 11,500 mm³ FL N27L69E2M2 Sed. Rate 40 mm/1st Hr</td>
</tr>
<tr>
<td>04/11/2002</td>
<td>No special finding</td>
<td>CD4/CD8 0.39</td>
<td></td>
</tr>
<tr>
<td>04/12/2002</td>
<td>Bronchopneumonia</td>
<td>CD4:716 CD8:2,743</td>
<td></td>
</tr>
<tr>
<td>25/08/2003</td>
<td>Four months of treatment</td>
<td>CD3:3,578 CD4/CD8: 0.26</td>
<td></td>
</tr>
<tr>
<td>03/12/2003</td>
<td>Diet related diarrhea</td>
<td>CD4 1,083 CD8 2,740</td>
<td></td>
</tr>
<tr>
<td>18/03/2004</td>
<td>Flu syndrome</td>
<td>CD3 3,864 CD4/CD8 0.4</td>
<td>WBC 10,400; Hct 31.5%; HGB 9.9/dl N24 M1 E4L71</td>
</tr>
<tr>
<td>25/06/2004</td>
<td></td>
<td></td>
<td>WBC 7,600 mm³; RBC 4.58 10⁶; HGB 9.3g/dl; HCT 30.2%; PLA 787 10³; MCV 66 μm³; TGMH 20.3 pg; MCCH 30.7 g/dl; N45 E3L52%; SR 30mm/H</td>
</tr>
<tr>
<td>02/09/2004</td>
<td>Enteritis</td>
<td>CD4:564 CD8:1,281CD3:1,940</td>
<td>WBC 7,200; Hct 28.1%; HGB 8.9g/dl N67L29 E0 M4</td>
</tr>
<tr>
<td>12/12/2004</td>
<td>Prurigo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/15/2005</td>
<td>Bronchopneumonia, Prurigo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/12/2005</td>
<td>Shingles in process of healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17/07/2006</td>
<td>Malaria, teeth decay</td>
<td>CD4 719(19%) CD8 1,784(47%) CD3 2,600(68%) R: 0.4</td>
<td></td>
</tr>
<tr>
<td>24/07/2006</td>
<td>No special findings</td>
<td>CD4 656(16%) CD8 1,805(43%) CD3 2,557(61%) R: 0.36</td>
<td></td>
</tr>
<tr>
<td>24/08/2006</td>
<td>Flu syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

disease advancement (CDC, 1994). Throughout CPDS treatment, the child did not experience any severe ailment episodes that could indicate a Stage 3 WHO pediatrics classification. Because of low weight, the child was considered at Stage 2 (WHO, 1990). The steadiness of the weight curve suggests a certain benefit from CPDS despite the nutritional insecurity generated by the advanced illness of the mother and early death of the father. The child’s weight slightly dropped at 36 months-old due to a shingles episode but recovered immediately to its previous upward trend as shown in the weight curve (Figure 1).

Evidence for episodes of fever was very scarce under CPDS treatment. Two fever episodes were recorded, at 2 and 8 months of follow-up, respectively, due to non-life-threatening bronchopneumonia and malaria episodes. The patient was not under Cotrimoxazole prophylaxis. In addition to the bronchopneumonia with fever, the only other observed episode of respiratory tract infection appeared to be from a flu syndrome as reported in Table 1. No lymph node enlargement was observed during the trial. The two diarrhea episodes observed were irrelevant, one of them related to diet. No tuberculosis, meningoencephalitis, or oral thrush episodes occurred (Yotebieng et al., 2010).

Hemoglobin was low particularly at the beginning of the follow up. At two months of CPDS treatment, hemoglobin was 7.5 g/dl. The values available up to 22 months of follow-up treatment were all below 10 g/dl. However, at any time the patient could require blood replacement. This multifactorial anemia was likely influenced by the poor nutritional status of the patient. Being a child in growth, the level of CD4 remained steady throughout CPDS uptake and did not drop (Weiser et al., 2011; Edmonds et al., 2012).

The child did not display an increase of weight during the 3-6 months interval in course of the therapy, as observed in the mean weight of the group in a previous study (Ndarabu et al., 2017); however, the weight did not drop into the red area of growth curve during the four years under CPDS treatment, which is up to 60-months old. This low weight for age in this case can be attributed to a deficient nutritional intake. During breastfeeding, the mother was already in cachexia with concordant, very advanced HIV-AIDS. Moreover, the socio-economic level of the housing where the child grew was one of the low-income. The data therefore suggests a protective effect of CPDS in the maintenance of weight of this child.
Figure 2. Chest X-ray in December 2002 with upper alveolar infiltrate at the beginning of Immunotherapy.

(Grassetti and Moro, 2012). The illness episodes he displayed were mainly made by rhinitis, enteritis, shingles, prurigo and mild bronchitis. The patient shifted to ART in 2006, when it became universally accessible. At the time of preparation of this paper, at age 17, he is still in first-line therapy made of 1 NNRTI + 2 NRTI, weighing 62 Kg at his last medical visit (September, 2018), with a height of 1.67 m as recorded in his medical history.

Interpretation of CPDS treatment results

Given the fact that, in Africa, 52% of untreated children born with HIV had died by age 2 (Newell et al., 2004), our interpretation of the studies described in this paper is that the survival of this child could likely be attributed to CPDS. This is consistent with the findings in our earlier study reviewing the multi-patient CPDS trial, which found the CPDS-treated group death rate at 23.5% compared to 23.3% of the ARV-treated group, for a 24-month follow-up period (Ndarabu et al., 2017). The rate of death among PLWH in D.R. Congo is still high despite availability of ARV, displaying a value of 24.1% (Catwaba et al., 2017). This has put the D.R. Congo at risk of missing the year 2020 90-90-90 targets (90% of all PLWH will know their HIV status; 90% of all PLWH will receive antiretroviral therapy and 90% of all PLWH receiving antiretroviral therapy will have viral suppression). Patients in the D.R. Congo display, for the two last target parameters, modest values of 42 and 31%, respectively (UNAIDS, 2017). Our clinical use of CPDS suggests that treatment with the compound could contribute substantially towards achieving the 2030 AIDS elimination target (UNAIDS, 2016) by adding immunomodulation to the viral suppression efforts (Martrus and Altfeld, 2016).

CONCLUSION

The steady clinical and biological profile of this child during the four years of CPDS treatment suggests a beneficial impact for this immunotherapeutic agent even in a very young patient. Thus, we retain high interest of exploring further the simultaneous use of ART and CPDS immunotherapy for a greater clinical and biological benefit of PLWH. In light of previous findings that CPDS can activate NK cells in standard models of NK cell-mediated cytotoxicity, the significant evidence for the role...
of activated NK cells for treating various infectious and malignant diseases, as presented in multiple reviews (Tomin et al., 2016; Goldfarb and Herberman, 1982), and increasingly specific evidence for a role for NK cell-mediated immunotherapy for control of AIDS/HIV (Garrido et al., 2018; Mavillo et al., 2005; Mikulak et al., 2017; Scully and Alter, 2016), the authors believe that additional investigation of the potential beneficial effects of CPDS immunotherapy on treatment of AIDS/HIV is justified.

Further investigation of CPDS also is warranted because this immunomodulator has a very low cost of goods and manufacture that would allow it to be pragmatically available to under-served and economically disenfranchised patient populations including those in the D.R. Congo. This is in stark contrast to currently available drugs that are often financially out of reach to patients, resulting in unmet medical needs. In sum, the data and economics both argue for further investigation of CPDS for its role as an immuno-modulator that could play a role in augmenting treatment of HIV/AIDS. Towards that end, the potential immunologic, mechanism of CPDS in regulating NK cell activities are undergoing more thorough investigation. This will be the subject of an additional communication.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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