Lipodystrophy induced by combination antiretroviral therapy in HIV/AIDS patients: A Belgrade cohort study

Gordana Dragović*, Dragana Danilović†, Aleksandra Dimić, Djordje Jevtović‡

*Institute of Pharmacology, Clinical Pharmacology and Toxicology, †Institute of Infective and Tropical Diseases “Dr Kosta Todorovic”, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ‡Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Abstract

Background/Aim. Highly active antiretroviral therapy (HAART) has led to dramatic reductions in mortality and morbidity of HIV/AIDS-patients. Lipodystrophy, a syndrome including peripheral fat wasting and central obesity, is well-documented side effect of HAART. The aim of this study was to evaluate the incidence of lipodystrophy, and to determine its risk ratios in a HIV/AIDS-cohort. Methods. This cross-sectional study included all the antiretroviral-naive HIV/AIDS patients commencing HAART from October 1, 2001 to October 1, 2010, at the HIV/AIDS Center, Institute of Infectious and Tropical Diseases, Belgrade, Serbia. Univariate and stepwise multivariate logistic regression analyses were used to determine the odds ratios (OR) with the confidence interval (CI) of 95%, in order to establish the relative risk for lipodystrophy. The Kaplan-Meier-method was used to determine the probability of development lipodystrophy over time. All statistical analyses were performed using SPSS software version using 0.05 as a p-threshold for the significance. Results. This study included 840 HIV/AIDS patients, 608 women and 232 men, followed for 5.6 ± 2.8 years. The prevalence of lipodystrophy was 69.2%. Univariate and stepwise multivariate regression analysis identified that the female gender, hepatitis C coinfection, AIDS diagnosis prior to HAART initiation, nucleoside-reverse-transcriptase-inhibitors and protease-inhibitors based regimens had a high risk for developing lipodystrophy in HIV/AIDS-patients (OR = 1.6, 95% CI = 1.1–3.49, p = 0.04; OR = 3.31, 95% CI = 1.3–6.8, p < 0.01; OR = 3.7, 95% CI = 1.7–6.1, p < 0.01; OR = 2.1, 95% CI = 1.7–3.3, p < 0.01; OR = 6.1, 95% CI = 4.1–9.7, p < 0.01, respectively). Conclusion. Despite much greater life expectancy of HIV/AIDS-patients, treatment-related toxicities still remain a major concern. Monitoring of lipodystrophy, as side effect of HAART, is particularly important.

Key words: lipodystrophy; incidence; risk factors; hiv; antiretroviral therapy, highly active; sex; hepatitis c.

Apstrakt

Uvod/Cilj. Visokoaktivna antiretrovirusna terapija (HAART) dovela je do značajnog smanjenja mortaliteta i morbiditeta kod bolesnika sa HIV/AIDS-om. Lipodistrofija, sindrom definisan perfervim gubitkom masnog tkiva, pružen istovremenom centralnom gojaznošću, predstavlja dokumentovani neželjniji efekat HAART-a. Cilj ovog istraživanja bio je da se utvrdi incidencija lipodistrofije i da se determinira potencijalni faktori rizika od njenog nastanka i razvoja kod pacijenata sa HIV/AIDS-om koji su lečeni HAART-om. Metode. Retrospektivnom studijom bili su obuhvaćeni svi HIV/AIDS pacijenti koji nikada ranije nisu bili lečeni HAART-om i koji su započinjali nažačenu terapiju u periodu od 01.10.2001. do 01.10.2010. u Centru za HIV/AIDS Instituta za infektivne i tropske bolesti, Beograd, Srbija. Unijavljajna i naknadna multivarijantna logistička regressija primenjena su da bi se utvrdila odnos šansi (OR) i interval poverenja od 95% (95% CI) u cilju procene relativnog rizika od razvoja lipodistrofije. Kaplan-Meierova analiza korištena je u cilju procene verovatnoće razvoja lipodistrofije tokom vremena. Sve korisničke statističke analize radene su primenom SPSS softvera, pri čemu je p < 0.05 smatrano statistički značajno. Rezultati. U studiji je bilo uključeno ukupno 840 HIV/AIDS-pacijenata, 608 muških i 232 ženskog pola, koji su pruženi 5,6 ± 2,8 godina. Prevalencija lipodistrofije iznosila je 69,2%. Unijavljajna i naknadna multivarijantna regresija analiza identifikovala su ženski pol (OR = 1,6; 95% CI = 1,1–3,49, p = 0,04), koja je utvrdila incidenciju lipodistrofije, ali i neke druge neželjene efekte ove terapije..PrintWriter.

Correspondence to: Gordana Dragović, Institute of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Dr Subotića 1/III; 11 000 Belgrade, Serbia. Phone: 065 27 21 180. E-mail: gozza@beotel.net
The use of highly active antiretroviral therapy (HAART), in treatment of human immunodeficiency virus (HIV) has led to dramatic reductions in mortality and morbidity of patients. From a very bad prognosis in its beginnings, HIV infection and acquired immunodeficiency syndrome (AIDS) meanwhile became the chronic disease, which can be treated, controlled and supervised. HAART usually consists of the combination of two drugs from the nucleoside reverse transcriptase inhibitors (NRTI) group, and a single drug from the protease inhibitors (PI) group (2 NRTIs + 1 PI) or of one non-nucleoside reverse transcriptase inhibitor (NNRTI). The latter combination (2 NRTIs + 1 NNRTI) is equally efficient as the first one, so that the PIs are often reserved for the later stages of the treatment due to their higher resistance barrier.

Lipodystrophy, a syndrome including peripheral fat wasting and central obesity, which in some patients may be followed with metabolic changes such as hyperlipidemia and glucose intolerance, or diabetes mellitus, is well-documented side effect of HAART. Changes in body composition include lipoatrophy, a complete or partial loss of adipose tissue predominantly in limbs and face and lipohypertrophy, which is pathological accumulation of adipose tissue in the omentum, mesenterium, retroperitoneum and pelvis, dorso-cervical region, including breast enlargement in women. Lipodystrophy was made on the basis of physical examination, by recognizing changes such as fat loss from face, arms and legs, and accumulation of fat in the abdominal and/or dorso-cervical region, including breast enlargement in women, as described in the European AIDS Clinical Society (EACS) guidelines.

The exclusion criteria were: simultaneous therapy with corticosteroids, anabolic steroids, as well as the treatment of some of the AIDS-related opportunistic infections, within 3 months before the lipodystrophy diagnosis. During the study period, 25 antiretroviral drugs were registered worldwide, of which the following were also registered in Serbia: zidovudine, didanosine, lamivudine, stavudine, zalcitabine and abacavir (from the NRTI group), nevirapine and efavirenz (from the NNRTI group), saquinavir, nelfinavir, indinavir, fosamprenavir, lopinavir/ritonavir, and ritonavir for boosting other PIs (from the PI group). Nelfinavir and indinavir were withdrawn in 2008. Enfuvirtide was introduced in 2007 for salvage regimens. Newer drugs, such as tenofovir/emtricitabine, tipranavir, atazanavir, etravirine, raltegravir, as well as maraviroc, were not included among the drugs reimbursed by the national health insurance system during the study period.

The immunological and virological responses to HAART were evaluated every 4–6 months by measuring plasma viral loads (pVL) and CD4+ T-cell counts. Due to shortages, HAART monitoring was not performed regularly, which led to the delay in the measurements of CD4+ T-cell counts and viral loads. CD4 cells were quantified by flow-cytometry. Plasma HIV-1 RNA loads were measured by quantitative reverse transcriptase polymerase chain reaction (ultrasensitive assay version 1.5, Roche Molecular Systems, Branchburg, NJ, USA), with a lower limit of detection of 50 copies/mL (1.7 log10).

All statistical analyses were performed using SPSS software version using 0.05 as a threshold for the significance. Possible associations between lipodystrophy and gender, age above 40, coinfection with hepatitis C virus, AIDS at HAART initiation and the type of HAART regimen, were tested. Univariate and stepwise multivariate logistic regression analyses were used to determine the odds ratios (OR), with the confidence interval (CI) of 95%, in order to establish the relative risk for the occurrence of lipodystrophy. The Kaplan-Meier product limit method was used to determine the probability of developing lipodystrophy over time.

The study was approved by the Clinical Center of Serbia Ethics Committee, Belgrade, Serbia.
Results

This study included 840 HIV/AIDS patients, followed for a mean period of 5.6 ± 2.8 years. There were 608 (72.4%) men and 232 (27.6%) women. The median age was 43.5 years (range: 22–58 years). Along with HIV, 216 (25.7%) patients were coinfected with hepatitis C virus (HCV), and 52 (6.2%) patients with hepatitis B virus (HBV). The median CD4+ cell count was 347 cells/mm³ (range: 183–455 cells/mm³).

HAART regimens included the following: combinations of two NRTIs as a treatment backbone, with one or two PIs (taken by 14.3% of all the patients), or one NNRTI (33.3%), and multiple combinations of drugs from all the classes (52.4%).

The prevalence of lipodystrophy was 69.2%. The overall estimated probability of developing lipodystrophy increased with time, reaching 100% after ten years of treatment, with median time of 7 years for the development of lipodystrophy in 50% of patients (Figure 1). In the subgroup of patients coinfected with HCV, the prevalence of lipodystrophy was 41%, as opposed to 25.8% among those without HCV (p < 0.01).

Fig. 1 – The estimated probability (Kaplan-Meier product limit method) of developing lipodystrophy over time.

Univariate logistic regression analysis (Table 1) showed that female gender, age above 40, HCV coinfection, AIDS at HAART initiation, and prolonged usage of NRTIs, were all associated with lipodystrophy. Among the NRTIs, multivariate logistic regression analysis indicated that highest risk for lipodystrophy was associated with the usage of stavudine, didanosine and zidovudine. In contrast with this, lamivudine and abacavir were not significant predictors (OR 2.1, 95% CI 1.6–3.9, p = 0.09; OR 3.3, 95% CI 1.7–4.1, p = 0.6, respectively). The usage of NNRTI based regimens carried a lower risk for lipodystrophy (OR 2.1, 95% CI 1.2–3.3, p < 0.01). The same analysis showed that the PI regimens were also associated with the development of lipodystrophy (OR 5.9, 95% CI 3.7–9.6, p < 0.001). The stepwise multivariate regression analysis identified that the PI based regimens had together with NRTI drugs, female gender, HCV coinfection, and AIDS diagnosis prior to HAART initiation, a high risk for developing lipodystrophy in HIV/AIDS patients (Table 1).

Discussion

Within the recognition that HIV production could be suppressed, but not eradicated, the focus of antiretroviral therapy in the mid-1990s was to convert the infection from uniformly fatal disease into a long term, manageable condition. This accomplishment was reported in 1998, with the seminal publication from the Multicenter AIDS Cohort Study (MACS), associating a dramatic drop in death rates from AIDS with the widespread application of HAART in the USA 1. However, as patients may potentially be exposed to HAART for decades, treatment-associated toxicities, such as lipodystrophy, remains a concern.

The frequency of lipodystrophy in the Belgrade cohort was 69.2%, which was in correlation with the results of Miller et al. 8. Some previous studies had shown a lower prevalence of lipodystrophy, but that was probably in connection with the lack of precise definition of the syndrome, and the fact that only the most severe cases had been registered 9–11.

We also showed that the probability of developing lipodystrophy increases with time, reaching 100% by 10 years of HAART and with the median time of 7 years for the development of lipodystrophy. Lipodystrophy identification had

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.6 (2.12–4.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Age above 40 (years)</td>
<td>1.9 (1.4–3.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>HCV coinfection</td>
<td>2.4 (1.8–4.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>AIDS at HAART initiation</td>
<td>1.6 (1.1–3.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>NRTIs (prolonged usage)</td>
<td>2.9 (1.4–5.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>d4T</td>
<td>6.7 (1.8–8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ddl</td>
<td>4.6 (2.2–6.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>AZT</td>
<td>2.2 (1.2–3.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>PIs</td>
<td>5.9 (3.7–9.6)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

HCV – hepatitis C virus; AIDS – acquired immunodeficiency syndrome; HAART – highly active antiretroviral therapy; NRTI – nucleoside reverse transcriptase inhibitors; d4T – stavudine; ddl – didanosine; AZT – zidovudine; PIs – protease inhibitors; OR – odds ratio; CI – confidence interval.
profound implications for the management of HIV/AIDS. Its recognition as a side effect of HAART led to the reevaluation of the appropriate time to start the therapy and also to various modifications in therapy of HIV.

Numerous cross-sectional studies and many prospective cohort studies analysed the occurrence of lipodystrophy, and attempted to determine the factors that cause it. In our study, both the age above 40 and AIDS diagnosis at HAART initiation were associated with lipodystrophy, but the age above 40 was not an independent predictor. Several studies have demonstrated that the older age and AIDS diagnosis prior to HAART initiation are the risk factors for lipodystrophy. There are conflicting data regarding the risks associated with gender. Martinez et al., in their study, found that the female gender is at higher risk for lipodystrophy. Thiebaut et al., on the other hand, came to the contrary conclusions, that the female gender was not in higher risk for lido distracted. Several other studies established HCV coinfection as an independent predictor of lipodystrophy, demonstrating the association of HCV co-infection with higher rates of lipodystrophy.

NRTIs, especially thymidine analogues, are known to cause mitochondrial toxicity. Given the similarities in function between HIV reverse transcriptase and human DNA polymerase, it is not surprising that nucleoside analogues are competitive inhibitors of human DNA polymerase-gamma, a key enzyme for mitochondrial DNA (mtDNA) replication. The accumulation of mtDNA deficits induces a deficient production of molecules devoted to the intramitochondrial synthesis of adenosine triphosphate (ATP). Once ATP production drops below a certain threshold, sudden mitochondrial dysfunction and then cellular damage occurs that can lead to cell death. Tissues and organs cannot function properly, and the damage becomes clinically apparent. The clinical use of NRTI has been associated with adverse effects caused by mitochondrial dysfunction, such as acute pancreatitis, myopathy, peripheral neuropathy, anemia, neutropenia, hepatic toxicity and hyperlactataemia/lactic acidosis. Our data demonstrate that the older age and AIDS diagnosis prior to HAART initiation are the risk factors for lipodystrophy.

Lipodystrophy syndrome, together with the insulin resistance, type 2 diabetes mellitus and hyperlipidemia develop a cluster of metabolic abnormalities, referred to as the metabolic syndrome. Metabolic syndrome, increases the cardiovascular risk and has great impact on life expectancy in HIV/AIDS patients.

Life style modifications and exercise training, antiretroviral switch strategies, pharmacological management (rosiglitazone, metformin, human growth hormone, human growth hormone–releasing factor, leptin, etc) and reconstructive surgery could be possible treatment options for lipodystrophy syndrome.

The initial enthusiasm of clinicians with HAART success, primarily because of the possibility of the long-term control of HIV replication, is suppressed with the new knowledge about the potential toxicity of antiretroviral drugs. For some patients lipodystrophy is only a cosmetic problem, but for others the very same problem may affect their future decisions on the treatment, making them cease the therapy or significantly reduce treatment compliance. As the result, the patients may experience rebound in viral load or the development of viral resistance. This would eventually lead to disease progression and even to an increased risk of disease transmission, possibly by a drug resistant viral strain.

Conclusion

Despite much greater life expectancy of HIV/AIDS patients, treatment related toxicities still remain a major concern. Monitoring of the side effects of highly active antiretroviral therapy, such as lipodystrophy is, particularly important.

Acknowledgments

The work was a part of the project (Grant No 175024) supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia together with the “European AIDS Treatment Network” (NEAT): LSHPCT – 2006-037570 within the FP 6 program.

REFERENCES


9. Freitas P, Carvalho D, Santos AC, Madureira AJ, Xerinda S, Martinec E, et al. Central/Peripheral fat mass ratio is associated with mitochondrial toxicity, which is not the case with PIs and NNRTIs. Moreover, NNRTI based HAART is less likely to induce lipodystrophy than the PI based HAART.
with increased risk of hypertension in HIV-infected patients. J Clin Hypertens (Greenwich) 2012; 14(9): 593–600.


