Le Infezioni in Medicina, n. 1, 103-105, 2019

Switch to rilpivirine improves diabetes in an elderly HIV-positive patient

Claudio Ucciferri[1,2], Zaira Di Rosa[2], Francesca Vignale[1], Jacopo Vecchiet[1], Katia Falasca[1]

[1]Clinic of Infectious Diseases, Department of Medicine and Science of Aging, University "G. d'Annunzio" Chieti-Pescara, Italy;
[2]Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Campobasso, Italy

SUMMARY

Glucose intolerance and diabetes are becoming increasingly common in HIV-infected patients in the cART era. Many factors are associated with the development of diabetes in HIV-infected individuals who receive cART, one of which is the assumption of specific antiretroviral classes or agents. We describe a case in a 72-year-old Caucasian man with long-term HIV infection. We observed the development of unbalanced diabetes treated with insulin and metformin which improved when we replaced zidovudine with rilpivirine. This switch improved diabetes to such an extent that insulin suspension was required. In several countries zidovudine has long been used due to its low cost, although several side effects have been observed, especially in the long term. In this case, the switch to rilpivirine was shown to be able to improve the toxicity of zidovudine on glucose metabolism, representing a good option to be used.

Keywords: drug toxicity, cART, antiretroviral therapy.

INTRODUCTION

Combination antiretroviral therapy (cART) has changed the survival in patients with HIV infection. The cART has reduced the morbidity and mortality of infection through the suppression of viral replication and the increase of CD4 cell counts, transforming HIV infection into a chronic disease [1, 2]. The remarkable increase caused by cART has been accompanied by a new increase in several clinical conditions. The illness related to chronic HIV treatment are now well known; the real life experience has shown that HIV-infected people develop metabolic disorders (like hypovitaminosis, type II diabetes (DM), dyslipidemia), and finally run into an increased risk for cardiovascular diseases [3-9]. Glucose intolerance and DM are becoming more common in HIV-infected patients in the era of cART [10]. In fact, cohort studies showed that HIV-infected individuals on cART had a higher incidence of DM than those not on cART or their HIV-uninfected counterparts [11]. In regard to factors associated with the development of DM in HIV-infected individuals receiving cART, several cohort studies yielded inconsistent results in terms of the relationship between DM and exposure to specific antiretroviral classes or agents. A few studies identified PI-based therapy as a key risk factor, while other studies concluded that exposure to nucleoside reverse transcriptase inhibitors (NRTIs), rather than PIs, was associated with incident DM [7, 11-13]. Several data reported that zidovudine has an important risk factor for developing DM [7-14]. In this report we describe the clinical case of partial reversible zidovudine related diabetes.

Case presentation

A 72 years old sedentary Caucasian man with HIV infection, heterosexual, with co-infection of occult HBV, no smoking, no metabolic disorders and BMI 23. The patient received diagnosis

Corresponding author
Katia Falasca
E-mail: k.falasca@unich.it

of HIV infection in 1998 with CD4 T cell nadir of 300 cell/mmc and cART treatment with AZT/3TC/IDV was started, Framingham risk score was 15%. The patient had a good adherence to treatment with regular follow-up and HIV-RNA undetectable. In 2007, it was decided to change the therapy, due to the onset of diabetes mellitus and kidney stones and new treatment has been set with AZT/3TC/ABC; metformin 3 g/die was started too, then, in 2012, was added insulin glargine 8 UI/die with improvement of glycated hemoglobin (HbA1c) at 42-53 mmol/mol mean levels (normal range 20-42 mmol/mol), c peptide was not measured. Some years after, a simplification to TDF+FTC+EFV was proposed to the patient for mild hypoatrophy of the limbs and dyslipidemia, but the patient has repeatedly refused it. The patient has never showed pancreatitis episodes. In September 2015 the patient showed an increasing level of fasting glucose, HbA1c (raising to 70 mmol/mol), urinary glucose become detectable, and insulin glargine was increased from 8 U.I. to 15 U.I. per day. Moreover, new diagnosis of grade 1 of hypertension was made and patients starts therapy with telmisartan 40 mg daily [15, 16]. In January 2016, the value of HBA1c was 68 mmol/mol, abnormal level in fasting glucose was revealed and urinary glucose was positive. According to this exam, the dosage of insulin glargine was increased at 20 UI/die. The patient did not take any drug interacting with AZT. In April 2016 the patient referred polyuria, moreover higher levels in fasting glucose and HBA1c 88mmol/mol were observed and, based on this element, the cART therapy was switched from AZT to RPV, no changing was applied to anti-diabetes therapy. In a few days, we observed an improvement in polyuria and in fasting glucose. One month later several episodes of hypoglycemia were reported, HBA1C was significantly decreased to 58 mmol/mol, the dosage of insulin glargine was decreased from 20 U.I. to 10 U.I. and metformin to 2550 mg/die. Although the adjustment of antidiabetic therapy, the patient referred in June a reduction but not a disappearance of episodes of hypoglycemia, so it was decided to suspend insulin glargine while metformin was continued at 2550 mg/die with suboptimal control in HBA1c (Table 1). The patient referred good compliance and virologic success throughout the period of observation during the follow-up. At last revelation the count of lymphocytes T CD4 was 561 cell/mmc and HIV-RNA <20 cp/mL.

DISCUSSION

We report the first case of reverse dysglycemic crisis zidovudine related. The onset of diabetes during cART therapy is related to multifactorial etiology. After 48 weeks of treatment with cART an increase of inflammatory markers was observed and it was related with elevated risk of diabetes [10, 17]. NRTIs are structural analogs of native nucleosides that must be phosphorylated intracellularly into their 5'triphosphate form before being incorporated into pro-viral DNA during its replication by reverse transcriptase. These drugs, in particular older timidine drugs, have been considered the main responsible of mitochondrial toxicity by the inhibition of Pol-γ with a significant decrease of mitochondrial DNA that produces a diminished synthesis of respiratory chain enzymes leading to alteration in MT function. NRTI inhibit the enzyme Pol-γ with different mechanism [18]. This alteration devoid of adverse reactions with different incidence and severities including myopathy, ataxia, depression, anemia, pancytopenia, nausea, dysphagia, pancreatitis, hypertension, nephrolithiasis, diabetes mellitus, infertility, lactic acidosis, lipodystrophy, and others. In several countries, zidovudine is still used for its low cost and long experience of use. Nevertheless, little data is available about the reversibility of the side effects [19]. A lot of studies have shown the reversibility of haematological effects or the improvement of the metabolic profile associated with the replacement of zidovudine with another NRTI [20]. It is likely that the aging of the population leads to an increased risk of complications with old drugs, which must be responded to with a rapid change in therapy. In the present case, the substitution of zidovudine with rilpivirine, a very well tolerated NNRTI, allowed to improve the glycidic imbalance shown by the patient as well to reduce the antidiabetic treatment. The therapeutic optimization of the patients, especially in elderly, must be carried out early in order to avoid long-term complications of the treatment. In case of appearance of side effects, the therapy should be modified as soon as possible to allow

a hospitalization, even partial damage related to zidovudine. The substitution of zidovudine with rilipivirine is shown to be able to partially solve the glucidic alteration of zidovudine.

Competing interests
The authors declare that they have no competing interests.

REFERENCES

[1] Wandeler G., Johnson L.F., Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. *Curr. Opin. HIV AIDS.* 11, 5, 492-500, 2016.
[2] van Sighem A.I., Gras L.A., Reiss P., Brinkman K., de Wolf F. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* 19, 24, 10, 1527-1535, 2010.
[3] Falasca K., Ucciferri C., Manzoli L., et al. Metabolic syndrome and cardiovascular risk in HIV-infected patients with lipodystrophy. *Int. J. Immunopathol. Pharmacol*. 20, 3, 519-27, 2007.
[4] Falasca K., Ucciferri C., Mancino P., Pizzigallo E., Calza L., Vecchiet J. Severe HIV-associated hypertriglyceridaemia treated with rosuvastatin plus omega-3 fatty acids. *Int. J. STD AIDS.* 20, 8, 580-581, 2009.
[5] Falasca K., Ucciferri C., Di Nicola M., Vignale F., Di Biase J., Vecchiet J. Different strategies of 25OH vitamin D supplementation in HIV-positive subjects. *Int. J. STD AIDS.* 5, 11, 785-792, 2014.
[6] Ucciferri C., Falasca K., Vignale F., Di Nicola M., Vecchiet J. Long term effect of switching to darunavir/ritonavir in HIV infected patients previously on protease inhibitor therapy. *Braz. J. Infect Dis.* 20, 4, 401-402, 2016.
[7] De Wit S., Sabin C.A., Weber R., et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care*. 31, 6, 1224-1229, 2008.
[8] Vecchiet J., Ucciferri C., Falasca K., Mancino P., Di Iorio A., De Caterina R. Antihypertensive and metabolic effects of telmisartan in hypertensive HIV-positive patients. *Antivir. Ther*. 16, 5, 639-645, 2011.
[9] Ucciferri C., Brescini L., Staffolania S., et al. Use of direct renin inhibitor in an HIV positive subject. *Infez. Med.* 20, 1, 49-51, 2012.
[10] Brown T.T., Cole S.R., Li X., et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch. Intern. Med*. 165, 10, 1179-1184, 2005.
[11] Ledergerber B., Furrer H., Rickenbach M., et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin. Infect. Dis.* 45, 1, 111-119, 2007.
[12] Justman J.E., Benning L., Danoff A., et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J. Acquir. Immune Defic Syndr.* 32, 3, 298-302, 2003.
[13] Tien P.C., Schneider M.F., Cole S.R., et al. Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study. *AIDS.* 21, 13, 1739-1745, 2007.
[14] Lo Y.C., Chen M.Y., Sheng W.H., et al. Risk factors for incident diabetes mellitus among HIV-infected patients receiving combination antiretroviral therapy in Taiwan: a case-control study. *HIV Med.* 10, 5, 302-309, 2009.
[15] Ucciferri C., Falasca K., Vecchiet J. Hypertension in HIV: Management and Treatment. *AIDS Rev*. 19, 4, 198-211, 2017.
[16] Ucciferri C., Falasca K., Vignale F., Di Nicola M., Vecchiet J. Long term effect of telmisartan in HIV-positive male patients with high blood pressure. *Braz. J. Infect. Dis*. 19, 6, 668-669, 2015.
[17] Brown T.T., Tassiopoulos K., Bosch R.J., Shikuma C., McComsey G.A. Association between] systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy. *Diabetes Care.* 33, 10, 2244-2249, 2010.
[18] Lewis W., Day B.J., Copeland W.C. Mitochondrial toxicity of NRTI antiviral drugs: an integrated cellular perspective. *Nat. Rev. Drug Discov.* 2, 10, 812-822, 2003.
[19] Iwata K., Ogawa W. Reversible diabetes mellitus induced by use of, and improved after discontinuation of, the antiretroviral medication zidovudine: a case report. *J. Med. Case Rep.* 11, 1, 157, 2017.
[20] Negredo E., Miro O., Rodriguez-Santiago B., et al. Improvement of mitochondrial toxicity in patients receiving a nucleoside reverse-transcriptase inhibitor-sparing strategy: results from the Multicenter Study with Nevirapine and Kaletra (MULTINEKA). *Clin. Infec.t Dis.*49, 6, 892-900, 2009.