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Enzalutamide and antiretroviral drugs: a challenge for clinicians

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ABSTRACT:

Objective: *Enzalutamide is a non-steroidal anti-androgen for metastatic prostate cancer. It has a consistent influence on several cytochromes' activity; therefore, co-administration of ART (antiretroviral therapy) is strongly contraindicated considering the high risk of virological failure.*

We are describing how we successfully used Therapeutic Drug Monitoring (TDM) to modify ART dosing in an HIV-infected patient affected by metastatic prostate cancer who needed long-term treatment with enzalutamide.

Keywords: *Enzalutamide, TDM, ART, HIV, Drug interactions.*

Abbreviations: *ART: antiretroviral therapy; cART: combined antiretroviral therapy; EACS: European AIDS Clinical Society; PSA: prostatic specific antigen; TDM: therapeutic drug monitoring; UGT1A1: UDP-glucorosil-transferasi A1.*

INTRODUCTION

Since the introduction of combined antiretroviral therapy (cART) the life expectancy of HIV-infected individuals has significantly improved. As a consequence, we are seeing more HIV patients at advanced age which are presenting corresponding comorbidities and therapies.

Prostate cancer is a typical aging-related tumour, whose incidence is not increased by a pre-existing HIV infection. Silverberg et al[1] observed prospectively 20.775 HIV-infected and 215.158 HIV-uninfected individuals and reported even a reduced relative risk (RR) for it in HIV people (RR = 0.8; $p = 0.012$). A recent review of the literature[2] involving more than 2.780 males with HIV/AIDS developing prostate cancer, seems to confirm the data, but the authors emphasized the existing heterogeneity among studies and the necessity to acquire further well-designed prospective studies before drawing conclusions.

However, the prognosis appears to be worse for HIV-infected individuals, as has been reported by two North American studies[3,4]. Coghill et al[3] observed in a retrospective cohort study of 288 HIV-infected patients with non-advanced-stage cancers of various types including prostate cancer a significant elevation in the overall mortality rate (for prostate cancer hazard ratio or HR 1.58; 95% CI 1.23-2.03; $p < .01$) and cancer-specific mortality (for prostate cancer HR 1.65; 95% CI 0.98-2.79; $p = .06$), compared with a cohort of 307.980 non-HIV patients that were matched by type of cancer and treatment. Suneja et al[4] reported a significantly higher proportion of HIV-infected patients that did not receive specific treatment for prostate cancer, compared with prostate cancer non-HIV patients. In the regression analysis of this study the factors low CD4 count, injection drug use and being Afro-American were factors associated with missing although indicated antineoplastic treatment in this population.

The Italian guidelines for HIV management of the year 2017[5] are recommending annual screening for prostate cancer for HIV-infected men above the age of 50 years by performing rectal digital examination and

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quantitative detection of the plasmatic prostatic specific antigen (PSA). The guidelines of the European AIDS Clinical Society (EACS) of 2020[6] are recommending a repeated detection of PSA only every 2-4 years, however they are highlighting the negative consequences of overdiagnosis and overtreatment compared to only a modest reduction in prostate cancer specific mortality when basing prostate cancer screening on PSA.

In advanced stage prostate cancer patients with metastasized disease the European guidelines for prostate cancer management[7] are recommending a novel panel of non-steroidal anti-androgens (apalutamide, darolutamide, enzalutamide). These agents reveal as a common side-effect an activation of several cytochromes (such as CYP3A4, CYP2C19 and CYP2C9) and enzymes (e.g., UGT1A1), with the potential to reduce the plasmatic concentrations of ART, which in turn may lead to subsequent virological failure. As a consequence, the European Medicines Agency in its product information e.g., on enzalutamide disadvises concomitant administration of enzalutamide and antiretroviral drugs[8].

We hereby describe how we successfully used TDM to modify ART dosing in an HIV-infected patient affected by prostate cancer who needed long-term treatment with enzalutamide.

CASE REPORT

In June 2020, a 57-year-old man with known HIV-1 infection, followed at our outpatient clinic, received a new diagnosis of metastatic prostate cancer. He regularly assumed ART since 2007, the year of the first diagnosis of HIV infection, obtaining stable viral suppression and good immunological recovery (CD4+ count was 618 cells/mm^3, 25.1%). The genotypic resistance test for HIV drugs performed at first diagnosis in 2007 showed no resistance and the ongoing ART was emtricitabine 200 mg/tenofovir alafenamide 25 mg/bictegravir 50 mg once a day. Co-morbidities were an occult HBV infection, arterial hypertension and dyslipidaemia, and co-medications were fenofibrate 145 mg once a day, pravastatin 20 mg once a day, cholecalciferol 25.000 orally twice a month. For his neoplastic condition, the urologist prescribed the subcutaneous monthly administration of the hormonal antineoplastic agent leuprolide (enantone) and the daily and long-term administration of enzalutamide. Due to the potential of enzalutamide to reduce plasmatic concentration of bictegravir, we replaced the ongoing therapy with darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg once a day, hoping to counterbalance the effect on CYP3A4 of cobicistat (inhibitor) and enzalutamide (inducer). Unfortunately, darunavir plasmatic reduction was substantial from day 1 to day 10 after this ART change (from 2423 ng/ml to 453 ng/ml). Consequently, we tried to change again the ART regimen, starting emtricitabine 200 mg/tenofovir alafenamide 20 mg once a day plus dolutegravir 50 mg twice a day. After a month of co-administration, dolutegravir plasmatic concentration, detected just before the morning drug assumption, was 2529 ng/ml. Even in the absence of an established plasmatic range of normal for dolutegravir, we considered this value adequate, referring to existing literature[9-11] and historical dataset of the laboratory which performed the plasmatic level detection. At the time of writing, which is 6 months after the commencement of co-administration of enzalutamide and ART, our patient maintains viral suppression and stable immunological defense.

DISCUSSION

We here present the use of TDM for ART when being co-administered with enzalutamide as a novel non-steroidal anti-androgen. The clinical experience and available literature on the use of TDM for ART are very scarce, despite the clinical relevance of both treatment regimens. We conducted a literature search on the topic when being confronted with the conflicting treatment regimens, which revealed only one case report[12] (digital library of the University of Brescia (Italy), keyword combination (HIV[Title/Abstract]) AND (enzalutamide[Title/Abstract]) with no limitations of publication time or languages).

Considering the increased life expectancy of HIV-infected individuals by the implementation of ART, and therefore the emergence of malignancies as an immediate cause of morbidity and mortality in HIV patients we believe that the use of TDM for ART when co-administering novel non-steroidal anti-androgens should be implemented. Similar recommendations have already been materialized for anti-tubercular drugs[13,14], antiepileptics[15], or immunosuppressants used after transplantations[16].

CONCLUSIONS

In HIV-infected individuals with advanced stage prostate cancers the use of TDM for ART when co-administering novel non-steroidal anti-androgens, e.g., enzalutamide, should be implemented.

Ethics approval and consent to participate:
As this study had a retrospective design and was based on routinely collected data, patients' informed consent was not required according to the Italian law (Italian Guidelines for classification and conduction of observational studies, established by the Italian Drug Agency, "Agenzia Italiana del Farmaco – AIFA" on March 20, 2008). Moreover, for this study we used the general authorization of the Italian Guarantor for the use of retrospective demographical and clinical data, which have been anonymized and treated according to Italian current laws. In addition, we contacted the patient who gave an informed consent for this publication.

Consent for publication:
Data were exported in an anonymized fashion.

Availability of data and materials:
Not applicable

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

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Authors' Contribution:
GG, II, and IEH clinically managed the patient. GG and GDF conducted the literature research. GG and II compiled the manuscript. All authors revised the manuscript and approved the final version.

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REFERENCES

1. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, Towner WJ, Dubrow R, Quesenberry CP Jr, Neugebauer RS, Abrams DI. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev 2011; 20: 2551-2559.
2. Sun D, Cao M, Li H, Ren J, Shi J, Li N, Chen W. Risk of prostate cancer in men with HIV/AIDS: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2021; 24: 24-34.
3. Coghill AE, Suneja G, Rositch AF, Shiels MS, Engels EA. HIV Infection, Cancer Treatment Regimens, and Cancer Outcomes Among Elderly Adults in the United States. JAMA Oncol 2019; 5: e191742.
4. Suneja G, Shiels MS, Angulo R, Copeland GE, Gonsalves L, Hakenewerth AM, Macomber KE, Melville SK, Engels EA. Cancer treatment disparities in HIV-infected individuals in the United States. J Clin Oncol 2014; 32: 2344-2350.
5. Linee Guida Italiane sull'utilizzo della Terapia Antiretrovirale e la gestione diagnostico-clinica delle persone con infezione da HIV-1. Edizione 2017. Società Italiana di Malattie Infettive e Tropicali – SIMIT. Available at <http://www.salute.gov.it/imgs/C_17_pubblicazioni_2696_allegato.pdf>. Access date 10/05/2021.
6. European AIDS Clinical Society (EACS) Guidelines. Edizione 2020. Available at <https://www.eacsociety.org/files/guidelines-10.1_30032021_1.pdf>. Access date 10/05/2021.
7. European guidelines for the management of prostate cancer. European Association of Urology. Available at <https://uroweb.org/guideline/prostate-cancer/>. Access date 10/05/21.
8. Enzalutamide (Xtandi) Summary of product characteristics. Available at <https://ec.europa.eu/health/documents/communityregister/2017/20170921138725/anx_138725_en.pdf>. Access date 01/03/2021.
9. Cattaneo D, Minisci D, Cozzi V, Riva A, Meraviglia P, Clementi E, Galli M, Gervasoni C. Dolutegravir plasma concentrations according to companion antiretroviral drug: unwanted drug interaction or desirable boosting effect? Antivir Ther 2017; 22: 353-356.
10. Dolutegravir (Tivicay). Clinical pharmacology review. Available at <https://www.fda.gov/files/drugs/published/N204-790-Dolutegravir-Clinpharm-PREA.pdf>. Access date 09/03/2021.
11. Calcagno A, Moltó J, Borghetti A, Gervasoni C, Milesi M, Valle M, Avataneo V, Alcantarini C, Pla-Junca F, Trunfio M, D'Avolio A, Di Giambenedetto S, Cattaneo D, Di Perri G, Bonora S. Older Age is Associated with Higher Dolutegravir Exposure in Plasma and Cerebrospinal Fluid of People Living with HIV. Clin Pharmacokinet 2021; 60: 103-109.
12. Nhean S, Bravo J, Sheehan NL, Walmsley S, Tilley D, Tseng AL. Successful use of the potent enzyme inducer enzalutamide in a treatment-experienced HIV-positive male with prostate cancer. AIDS 2018; 32: 2640-2642.
13. Newman M, Foisy MM, Ahmed RA. The Use of Therapeutic Drug Monitoring in Complex Antituberculous and Antiretroviral Drug Dosing in HIV/Tuberculosis-Coinfected Patients. J Int Assoc Provid AIDS Care 2015; 14: 295-299.
14. Wilby KJ, Ensom MH, Marra F. Review of evidence for measuring drug concentrations of first-line antitubercular agents in adults. Clin Pharmacokinet 2014; 53: 873-890.
15. Cattaneo D, Baldelli S, Cozzi V, Fusi M, Atzori C, Micheli V, Filice C, Gervasoni C. Drug-Drug Interactions Between Antiretrovirals and Carbamazepine/Oxcarbazepine: A Real-Life Investigation. Ther Drug Monit 2020; 42: 330-334.
16. Cattaneo D, Puoti M, Sollima S, Moioli C, Foppa CU, Baldelli S, Clementi E, Gervasoni C. Reduced raltegravir clearance in HIV-infected liver transplant recipients: an unexpected interaction with immunosuppressive therapy? J Antimicrob Chemother 2016; 71: 1341-1345.