European Journal of Internal Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Epidemiological trends of deep venous thrombosis in HIV-infected subjects (1997–2013): A nationwide population-based study in Spain

Alejandro Alvaro-Meca[a], Pablo Ryan[b], Esther Martínez-Larrull[c], Dariela Micheloud[c], Juan Berenguer[d,e], Salvador Resino[f,*]

[a] Unidad de Medicina Preventiva y Salud Pública, Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain
[b] Servicio de Medicina Interna, Hospital Universitario Infanta Leonor, Madrid, Spain
[c] Servicio de Urgencias, Hospital General Universitario "Gregorio Marañón", Madrid, Spain
[d] Unidad de Enfermedades Infecciosas/VIH, Hospital General Universitario "Gregorio Marañón", Madrid, Spain
[e] Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[f] Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain

ARTICLE INFO

Keywords:
AIDS
Hepatitis C
Deep venous thrombosis
Cardiovascular disease
Incidence
ICD9CM codes

ABSTRACT

Background: Chronic infections may be a triggering factor as well as a risk factor of deep venous thrombosis (DVT). The purpose of this study was to analyze the epidemiological trends of hospital admissions related to DVT in human immunodeficiency virus (HIV)-infected patients during the combination antiretroviral therapy (cART) era, in relation to hepatitis C virus (HCV) serological status.

Methods: We performed a retrospective study using the Spanish Minimum Basic Data Set. We selected HIV-infected subjects over 15 years old with a hospital admission and DVT diagnosis (ICD-9-CM codes: 453.4x and 453.8x) between 1997 and 2013. Patients were classified according to HCV serology. We estimated the incidence (events per 100,000 patient-years) in four calendar periods (1997–1999, 2000–2003, 2004–2007, and 2008–2013).

Results: Overall, the incidence of DVT-related hospitalizations had a significant upward trend in all HIV-infected patients ($P < 0.001$), with significant differences between 1997–1999 and 2008–2013 [49.5 vs. 88.1 ($P < 0.001$)]. Moreover, the incidence was higher in HIV-monoinfected patients than in HIV/HCV-coinfected patients during the entire follow-up ($P < 0.001$). However, the incidence had a significant downward trend in HIV-monoinfected patients ($P = 0.002$) and a significant upward trend in HIV/HCV-coinfected patients ($P < 0.001$). Specifically, the incidence of DVT-related hospitalizations in HIV-monoinfected patients significantly decreased from 1997–1999 to 2008–2013 [142.7 vs. 103.1 ($P = 0.006$)], whereas in HIV/HCV-coinfected patients, the incidence increased from 8.4 (1997–1999) to 70.7 (2008–2013) ($P < 0.001$).

Conclusions: Our findings suggest that DVT is an emerging health problem among HIV-infected patients, with increasing incidence during the first 17 years after the introduction of cART, particularly in HIV/HCV-coinfected patients.

1. Introduction

Deep venous thrombosis (DVT) is a common and serious cardiovascular disease associated with higher hospital admission rates and death [1–3]. Venous thromboembolism [pulmonary embolism (PE) or DVT] may occur by a combination of factors that are specific to a given patient (anomalies of hemostasis, chronic diseases, age, etc.) and precipitating factors (surgery, catheterization, acute venous stasis, acute pathologies, etc.) [1,4]. Chronic infections may be a triggering factor that may induce immune cell activation, inflammation-associated protein synthesis by the liver, and modification of the coagulation and fibrinolysis pathways and thus increase the risk of DTV [4].

The widespread use of combination antiretroviral therapy (cART) has resulted in a dramatic reduction of illness and mortality in human immunodeficiency virus (HIV)-infected individuals, and HIV infection has become a chronic manageable disease [5]. However, non-AIDS-related conditions, such as cardiovascular disease, have become the most frequent causes of hospitalization and death in HIV-infected persons [5]. Regarding venous thromboembolism, previous studies have reported a higher risk of venous thromboembolism in HIV-infected

* Corresponding author at: Centro Nacional de Microbiología, Instituto de Salud Carlos III (Campus Majadahonda), Carretera Majadahonda-Pozuelo, Km 2.2, 28220 Majadahonda, Madrid, Spain.
E-mail address: sresino@isciii.es (S. Resino).

http://dx.doi.org/10.1016/j.ejim.2017.10.012
Received 19 July 2017; Received in revised form 9 October 2017; Accepted 16 October 2017

patients than in the general population [6–12], suggesting that HIV infection is a risk factor for venous thromboembolism. Among the factors that increase the risk of venous thromboembolism in HIV-infected individuals are HIV replication itself, cART, the existence of an active opportunistic infection, and low levels of CD4 + T-cells, all of which may induce persistent systemic inflammation, triggering upregulation of procoagulant factors and downregulation of anticoagulant and fibrinolysis factors [4,13].

Chronic hepatitis C (CHC) has also been associated with a higher risk of thrombotic events [14,15], particularly in cirrhotic patients [16]. The link between hepatitis C virus (HCV) infection and venous thromboembolism might be explained by several factors that may exist in patients with CHC, such as a direct endothelial damage by the HCV virus, and subsequent tissue factor activation, altered fibrinolysis and increased platelet aggregation and activation [17]. Additionally, cirrhotic patients have an alteration in portal microcirculation that may lead to thrombin activation, platelet aggregation, and clot formation [17].

Globally around 20% of HIV-positive patients have chronic hepatitis C, mainly because HIV and HCV are transmitted via the same routes [18]. HIV/HCV-coinfected subjects are an important clinical subgroup that may differ from HIV-monoinfected patients in terms of risk factor distribution and inflammatory profile [10]. Furthermore, the interactions among HIV, HCV and cART are also associated with several metabolic disorders that may increase the risk of thrombotic events [19]. In fact, an increased risk of cardiovascular disease in HIV/HCV-coinfected subjects in comparison to HIV-monoinfected subjects has been reported [20,21].

The aim of this study was to analyze the epidemiological trends of hospital admissions related to DVT in HIV-infected patients during the cART era, with particular attention to HIV/HCV-coinfected patients.

2. Materials and methods

2.1. Study population

We carried out a retrospective study. We reviewed the computerized data from the Spanish Minimum Basic Data Set (MBDS) between 1997 and 2013, finding HIV-infected patients aged 16 years and older with a hospital admission and a DVT diagnosis. The study period was from January 1, 1997 to December 31, 2013, which was subdivided into four calendar periods according to the widespread use of cART among HIV-infected subjects [22]: a) from 1997 to 1999 (1997–1999); b) from 2000 to 2003 (2000–2003); c) from 2004 to 2007 (2004–2007); and d) from 2008 to 2013 (2008–2013).

Data of patients with a diagnosis of DVT were obtained from the records of the Minimum Basic Data Set (MBDS), provided by the Ministry of Health Social Services and Equality (MSSSI). The MBDS is a clinical and administrative database containing clinical information recorded at the time of hospital discharge, which has an estimated coverage of 92% of hospital discharges registered in hospitals in Spain (84.14% from public hospitals and 15.86% from private hospitals) [23]. The National Health System (NHS) provides free medical care to 99.5% of the Spanish population, although those persons not covered by the NHS still may be attended to at the public hospitals.

The MBDS provided the encrypted patient identification number, sex, date of birth, dates of hospital admission and discharge, patients' residential postal code, medical institutions providing the services, the diagnosis and procedure codes according to the *International Classification of Diseases, 9th ed, Clinical Modification* (ICD-9-CM), and outcome at discharge. The MDBS includes up to 14 discharge diagnoses and up to 20 procedures performed during the hospital stay. The Spanish MSSSI sets standards for record-keeping and performs periodic audits.

2.2. Ethics statement

This study involves the use of patient medical data from the Spanish MBDS, which is hosted by the MSSSI. The MBDS is regulated by Spanish law, which explains how institutions are required to utilize health-related personal data. As described in detail previously [24], the data were treated with full confidentiality according to Spanish legislation. The MSSSI evaluated the protocol of our investigation and considered it to meet all ethical aspects according to Spanish legislation. Given the anonymous and mandatory nature of the dataset, it was not necessary to obtain informed consent. Furthermore, our study was approved by the Research Ethic Committee (Comité de Ética de la Investigación y de Bienestar Animal) of the Instituto de Salud Carlos III (Madrid, Spain).

2.3. ICD-9-CM codes selected and study groups

We selected subjects who were coded in the MBDS with a DVT diagnosis [453.4x and 453.8x (see Table S1)], according to the criteria of White et al. [25]. ICD-9-CM codes were also used for defining the viral infection status: i) HIV infection (042 or V08); ii) HCV infection (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, 070.7x, or V02.62); iii) HBV infection (ICD-9-CM codes 070.2x, 070.3x, or V02.61) (see Table S1). Accordingly, we categorized patients as: i) HIV-infected (all HIV-infected subjects with or without HCV coinfection); ii) HIV-monoinfected (subjects exclusively infected with HIV); iii) HIV/HCV-coinfected (subjects coinfected with HIV and HCV). HBV infection was a criterion for exclusion.

2.4. Outcome variables

Hospitalization was defined as a discharge record in the MBDS with a DVT diagnosis. The index episode of a patient was the first hospital discharge encoded in MBDS with a DVT diagnosis. Patients who were readmitted with a DVT diagnosis were not counted as a new episode of DVT.

The outcome variables analyzed in this study were; 1) first DTV-related hospital admission and 2) death among patients with a DTV-related hospital admission.

2.5. Reference populations

The estimation of the number of people living with HIV/AIDS in Spain (see Table S2) was provided by the National Centre of Epidemiology (Instituto de Salud Carlos III, Madrid, Spain) [26]. The number of people monoinfected with HIV and coinfected with HIV and HCV in Spain was estimated using the results from the hospital survey of HIV/AIDS patients, a second-generation surveillance system in people living with HIV coordinated by the National Centre of Epidemiology [27], and the reports of two Spanish national cohorts: the “Grupo de Estudio de Sida” (GeSIDA) [28] and the “Asociación Médica VACH de Estudios Multicentricos (AMVACH)” [29].

2.6. Statistical analysis

The incidence (new DVT diagnosis in the MBDS) was estimated as the ratio between the number of events within each calendar period and the number of persons at risk within each calendar period. The case fatality rate (CFR) was estimated as the proportion between the number of DVT-related deaths and the number of hospitalized patients with DVT diagnosis.

Categorical data and proportions were analyzed using chi-squared test or Fisher's exact test, as required. *T*-test or Mann-Whitney *U* test was used to compare continuous variables. Temporal trends of incidence rates of DVT were evaluated using the Extended Mantel Haenszel Chi Square for linear trend. We also calculated the odds for in-hospital death in patients with DVT diagnosis according to calendar