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Predictive factors of clinically significant drug–drug interactions among regimens based on protease inhibitors, non-nucleoside reverse transcriptase inhibitors and raltegravir☆

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ABSTRACT

Background and objective: To determine the prevalence and types of clinically significant drug–drug interactions (CSDI) in the drug regimens of HIV-infected patients receiving antiretroviral treatment.
Material and methods: Design: retrospective review of database. *Centre*: Hospital Universitario Severo Ochoa, Infectious Unit. *Participants*: one hundred and forty-two participants followed by one of the authors were selected from January 1985 to December 2014. *Data collection*: from their outpatient medical records we reviewed information from the last available visit of the participants, in relation to HIV infection, comorbidities, demographics and the drugs that they were receiving; both antiretroviral drugs and drugs not related to HIV infection. We defined CSDI from the information sheet and/or database on antiretroviral drug interactions of the University of Liverpool (http://www.hiv-druginteractions.org) and we developed a diagnostic tool to predict the possibility of CSDI. By multivariate logistic regression analysis and by estimating the diagnostic performance curve obtained, we identified a quick tool to predict the existence of drug interactions.
Results: Of 142 patients, 39 (29.11%) had some type of CSDI and in 11.2% 2 or more interactions were detected. In only one patient the combination of drugs was contraindicated (this patient was receiving darunavir/r and quetiapine). In multivariate analyses, predictors of CSDI were regimen type (PI or NNRTI) and the use of 3 or more non-antiretroviral drugs (AUC 0.886, 95% CI 0.828–0.944; $P = .0001$). The risk was 18.55 times in those receiving NNRTI and 27.95 times in those receiving IP compared to those taking raltegravir.
Conclusions: Drug interactions, including those defined as clinically significant, are common in HIV-infected patients treated with antiretroviral drugs, and the risk is greater in IP-based regimens. Raltegravir-based prescribing, especially in patients who receive at least 3 non-HIV drugs could avoid interactions.

Factores predictivos de las interacciones farmacológicas clínicamente significativas en los pacientes tratados con regímenes basados en inhibidores de proteasa, inhibidores de transcriptasa inversa no nucleósidos y raltegravir

Palabras clave:
Virus de inmunodeficiencia humana
Interacciones farmacológicas
Tratamiento antirretroviral

RESUMEN

Fundamento y objetivo: Determinar la prevalencia y los tipos de interacciones farmacológicas clínicamente significativas (IFCS) en los regímenes farmacológicos de los pacientes infectados por VIH que están recibiendo un tratamiento antirretroviral, y desarrollar una herramienta diagnóstica que pueda predecir la posibilidad de una IFCS.

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Material y métodos: Diseño: revisión retrospectiva de bases de datos. *Centro:* Hospital Universitario Severo Ochoa, Unidad de Infecciosas. *Participantes:* 142 participantes seguidos por uno de los autores fueron seleccionados desde enero de 1985 hasta diciembre de 2014. *Recogida de datos:* recogimos en la última visita disponible de los participantes información relacionada con la infección VIH, las comorbilidades, los datos demográficos y los fármacos que estuvieran recibiendo, tanto los antirretrovirales como aquellos no relacionados con la infección VIH. Se definió la existencia de IFCS por la información de la ficha técnica y/o la base de datos de interacciones de fármacos antirretrovirales de la Universidad de Liverpool (http://www.hiv-druginteractions.org). Mediante el modelo de análisis multivariable de regresión logística y con la estimación de la curva de rendimiento diagnóstico obtenida identificamos una herramienta que nos pudiera predecir la existencia de interacciones farmacológicas.
Resultados: De 142 pacientes, 39 (29,11%) tenían algún tipo de IFCS y en 11,2% se detectaron 2 o mas interacciones. Solo en un paciente la combinación de los fármacos estaba contraindicada (este paciente estaba recibiendo darunavir/r y quetiapina). En el análisis multivariable, los factores predictores de IFCS fueron el que estuvieran recibiendo un régimen basado en IP o ITINAN y la presencia de 3 o más fármacos no antirretrovirales (AUC 0,886, IC 95% 0,828-0,944; p = 0,0001). El riesgo fue 18,55 veces en aquellos que recibían ITINAN y 27,95 veces en los que recibían IP con respecto a aquellos que tomaban raltegravir.
Conclusiones: Las interacciones farmacológicas, incluyendo aquellas definidas como clínicamente significativas, son frecuentes en pacientes infectados por VIH tratados con antirretrovirales, y este riesgo es mayor en los regímenes basados en IP. Prescribiendo regímenes basados en raltegravir, especialmente en pacientes que reciben al menos 3 fármacos no relacionados con el VIH, se podrían evitar interacciones.

Introduction

The latest GeSIDA (AIDS Study Group) clinical guidelines[1] update recommends the use of at least 3 active drugs to create an antiretroviral regimen for HIV-infected patients. Regarding the priority antiretroviral regimen, the GeSIDA guidelines recommend two nucleoside reverse transcriptase inhibitors in combination with one of the two integrase transfer inhibitors: dolutegravir (DTV) or raltegravir. This recommendation was considered not only in terms of efficacy and toxicity of different regimens observed in clinical trials, but the possible occurrence of drug interactions of clinical significance. We have references showing that HIV-infected patients frequently receive between 6 and 10 drugs,[2] and that the risk of clinically significant drug interactions (CSDI) in patients receiving high activity antiretroviral therapy (ART) can approach 50%. Other studies have reported that the side effects that sometimes appear are the result of interactions with antiretroviral drugs.[3,4] A recent review by Manzardo et al.[5] described that interactions may be responsible for serious damage that can compromise the lives of patients. It also highlighted the fact that clinicians, especially those who do not deal directly with HIV-infected patients, should know about these interactions. Clinical signs and symptoms of ergotism, rhabdomyolysis, cardiac arrhythmias, excessive sedation, severe hypotension or Cushing's syndrome have been described as a result of interactions. The implications between antiretrovirals and other drugs in special situations are reviewed in the same publication, such as concomitant administration of cytostatics, immunosuppressants used in solid organ transplantation or patients receiving new treatments for hepatitis C.

Initiatives to detect interactions have been developed by means of new information technology tools. Thus, the electronic prescription project in Catalonia[6] is working on developing a comprehensive medication plan containing details of all the drugs prescribed to a patient, improving coordination between levels of care.

After the introduction of antiretroviral therapy (ART) and the subsequent increase in life expectancy, the comorbidities and mortality pattern of HIV-infected persons has changed. The attention to these patients has shifted from the care of opportunistic infections and malignancies associated with AIDS to the toxicities and interactions related to the use of antiretroviral drugs.

Only a few studies have[2,7–10] provided quantified CSDI risk information related to the most common antiretroviral regimens. We will try to quantify this risk with this study, comparing the CSDI between regimens based on protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI) or raltegravir as sole nucleoside reverse transcriptase inhibitor (NRTI), and build a tool for predicting CSDI risk among HIV-infected patients receiving a regimen based on one PI, NNRTI or NRTI during the study period.

Methods

The cohort of the Severo Ochoa Hospital[a] is prospective; includes new diagnoses of HIV infection in over 16 year olds and consists of 450 patients. Participants include those with at least one visit from January 1985 to December 2014. Participants were categorized into 3 age groups: <50, 50–64 and ≥65.

To ensure the reliability of the information we have only selected patients under follow-up by one of the authors. The collection protocol for the cohort database was approved by the local CREC.

Information related to HIV infection (CD4 count, CD4/CD8 ratio and HIV viral load), comorbidities, demographics, such as age, ethnicity, sex and anthropometric measures, and drugs being administered, both antiretrovirals as well as those unrelated to HIV infection was collected for the study on the last visit of the participants. No patient was being treated with direct-acting antivirals for hepatitis C because data collection had been prior to the authorization of these drugs. The CSDI classification used includes 2 categories: (1) combination which is contraindicated by the SmPC and/or the database of antiretroviral drugs interactions at the University of Liverpool (http://www.hiv-druginteractions.org) or evidenced by its high potential for side effects, and (2) a combination that needs a dose adjustment.

For statistical analysis of interactions, participants were grouped based on whether they had significant interactions. The difference in age, number of comorbidities and the number of antiretrovirals and non-antiretroviral drugs was determined with the Mann–Whitney *U* test, while the differences in sex, race,

[a] The cohort of HIV-infected patients from the Severo Ochoa Hospital is part of the COMESEM cohort, which also includes the Alcalá de Henares, Móstoles and Getafe university hospitals, and Fuenlabrada and Alcorcón foundations. The COMESEM cohort has obtained a favorable report from the Alcalá de Henares University Hospital CREC.