P623

Case-control study of genetic determinants of agranulocytosis associated with the use of metamizol and beta-lactamic antibiotics.

L Ibáñez, L Vendrell, M Molokhia, A Carvajal, E de la Banda, M Durán, E Montané, E Orna, C Pedros, R Puig, M Sabaté, E Sancho, A Vallano, E Palou. *[1]Vall d'Hebron University Hospital, Clinical Pharmacology. 08029, Spain, [2]Autonomous University of Barcelona, Pharmacology, Therapeutics and Toxicology.08193, Spain, [3]Vall d'Hebron University Hospital, Clinical Pharmacology. 08029, Spain, [4]Autonomous University of Barcelona, Pharmacology, Therapeutics and Toxicology.08193, Spain, [5]King's College, Division of Health and Social Care Research. SE1 3QD, UK, [6]Valladolid University, Pharmacoepidemiology Institute. 47005, Spain, [7]Bellvitge University Hospital, Hematology Laboratory. 08907, Spain, [8]Valladolid University, Biology and Genetics Institute.47005, Spain, [9]Trias i Pujol University Hospital, Clinical Pharmacology.08916, Spain, [10]Trias i Pujol University Hospital, Hematology Laboratory. 08916, Spain, [11]Bellvitge University Hospital, Clinical Pharmacology.08907, Spain, [12]Catalan Pharmacology Institute (FICF) Foundation, Clinical Pharmacology. 08029, Spain, [13]Vall d'Hebron University Hospital, Clinical Pharmacology. 08029, Spain, [14]Vall d'Hebron University Hospital, Hematology.08029, Spain, [15]Bellvitge University Hospital, Clinical Pharmacology.08907, Spain, [16]Catalan Health Department, Immunology and Molecular Diagnosis Laboratory (LIRAD). 08005, Spain*

Introduction: Though agranulocytosis presents a low incidence (3.5 per million per year), it is a serious condition with a case-fatality rate of around 10%. In a high proportion of cases, it is associated with drugs; metamizol and beta-lactamic antibiotics are the most frequently involved drugs[1] The fact that so few patients develop agranulocytosis after ingesting a potentially causative drug may indicate that genetic factors could play a role in its pathogenesis. Significant genetic associations have been identified in the major histocompatibility complex for hypersensitivity reactions associated with several drugs, and some of them have been recognized in drug induced agranulocytosis. The HLA system has been the main hypothesized region: a) gene variants of the HLA-DQB1 has been implicated in the pathogenesis of clozapine[2]; b) HLA A, B7 DQ1 was suggested to be associated with metamizol[3] although it has not been replicated.

Objectives: To present the methods and preliminary results on the collection of DNA for the pharmacoepidemiological study on genetic determinants of agranulocytosis associated with metamizol and beta-lactamic antibiotics. The study aims to compare the allelic distribution of HLA (A,B, DRB1, DBQ1) in the agranulocytosis cases associated with the use of metamizol or/and beta-lactamic antibiotics with that of their controls. As an additional objective the elastase 2 neutrophil genes related to mendelian forms of congenital agranulocytosis will be analyzed in the cases only.[4]

Methods: Design: Case-control study. Potential cases are patients with <500/mm^3 granulocytes. Retrospective and prospective cases are identified from the AG network in Barcelona (1980-) and the Eudragene collection.[5] Sample size:90 cases and 180 controls are considered to estimate an OR= 5 if the allelic frequency is at least 5% (Gauderman WJ, Morrison JM. QUANTO 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies, http://hydra.usc.edu/gxe, 2006).Sex and ethnicity/age matched controls will be selected. HLA will be determined by sequence-specific oligonucleotide probe PCR using the Luminex microbead technology. The software SKDM will be applied to compare the HLA allelic frequencies (two-sided Fisher test and Bonferroni correction).[6] Causality assessment is performed with the WHO algorithm.

Results: In the period January 1999-December 2010 147 retrospective cases were identified; of those 79(54%) are exposed to the study drugs. Blood samples were collected in 14(18%) cases (6 beta-lactamic antibiotics, 4 metamizol and 4 both drugs). Out of 18 prospective cases (up to 31/12/2011) 13(72%) were exposed to the study drugs. Blood samples were collected in 6(46%), (3 beta-lactamic antibiotics and 3 metamizol). Of these 20 cases with available blood samples, 11(55%) are women and 9(45%) men. 19 additional cases will be contributed by the Eudragene collection (3 beta-lactamic antibiotics, 9 metamizol, 7 both drugs).

Conclusions: Case-control design is an efficient approach to study genetic determinants of rare diseases associated to the use of drugs but national and international collaborative networks are needed. Both prospective and retrospective approaches are advisable for collecting samples for genetic studies of rare adverse drug effects.

References

1. Ibáñez L, Vidal X, Ballarín E, Laporte JR. Population-Based Drug-Induced Agranulocytosis. Arch Intern Med. 2005; 165:869-74

2. Chowdhury NI, Remington G, Kennedy JL. Genetics of antipsychotic-induced side effects and agranulocytosis. Curr Psychiatric Rep 2011; 13:156-65

3. Vlahov V, Bacracheva N, Tontcheva D, Naumova E, Mavrudieva M, Ilieva P, Michailova A. Genetic factors and risk of agranulocytosis from metamizol. Pharmacogenetics 1996;6:67-72

4. Dale DC, Person RE, Bolyard AA, Aprikyan AG, Bos C, Bonilla MA, Boxer LA, Kannourakis G, Zeidler C, Welte K, Benson KF, Horwitz M. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. Blood 2000; 96:2317-22

5. Molokhia M, McKeigue P. EUDRAGENE: European collaboration to establish a case-control DNA collection for studying the genetic basis of adverse drug reactions. Pharmacogenomics 2006; 7:633-8

6. Kanterakis S, Magira E, Rosenman KD, Rossman M, Talsania K, Monos DS. SKDM human leukocyte antigen (HLA) tool: A comprehensive HLA and disease associations analysis software. Hum Immunol. (2008) 69:522-5.