The Utility of HLA-DR Genotypification As a Complementary Tool to Discriminate Undifferentiated and Rheumatoid Arthritis Patients in Early Arthritis.

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Background/Purpose: Only half of patients with undifferentiated arthritis (UA) will progress to rheumatoid arthritis (RA) after two years of follow-up. Particular human leukocyte antigens class II-DR (HLA-DR) alleles have been associated with a higher risk to develop RA, however these alleles may vary among ethnic groups. The aim of our study was to investigate the frequency of HLA-DR alleles and evaluate the association with the development of rheumatoid arthritis in an early arthritis cohort in Latin America.

Methods: We designed a case-control study. Cases were defined as patients with diagnosis of RA from an early arthritis cohort (_2 years of disease duration). Two control groups were selected. First group was obtained from the mentioned cohort and included patients with UA. The second control group was obtained from the national register of cadaveric organ donors (Healthy Subjects, HS). HLA-DR genotypes frequencies were estimated for each group. We calculated the odds ratio (OR) to develop RA in general population and undifferentiated arthritis. Statistical analysis was performed with two-tailed Pearson's chi-squared test with Bonferroni adjustment (pvalue after Bonferrroni adjustment, Pc). A stepwise logistic regression model using RA vs UA diagnosis as dependent variable was performed to identify the association of HLA-DR alleles and RA development in patients with UA, adjusted by smoking, gender and presence of rheumatoid factor (variable significance entry criteria P _ 0.15). A p-value less than 0.05 was considered statistically significant.

Results: We included a total of 1859 subjects: AR_347; UA_52; Cs_1460. When comparing with HS, RA patients had an increased frequency of DR4 [RA_50% vs HS_31%, OR 2.3 (1.7 – 2.8), Pc_0.0001], DR9 [RA_12% vs HS_7%, OR 1.9 (1.3 – 2.8), Pc_0.02], and lower frequency of DR7 [RA_13% vs 21%, OR 0.6 (0.4 – 0.8), Pc_0.02], DR11 [RA_10% vs 21%, OR 0.4 (0.3 – 0.6), Pc_0.0001], DR15 [RA_9% vs 15%, OR 0.5 (0.4 – 0.8), Pc_0.04]. Among patients with early arthritis, being heterozygote or homozygote for DR-4 allele could not differentiate between patients with RA and UA. On the other hand, patients with UA showed higher frequency of DR7, DR11 and DR15 than RA (23%, 21%, 17% vs 13%, 11% 9%, respectively), but did not reach statistical significance after adjustment for multiple comparisons. Stepwise regression indicated that the presence of DR15 was significantly associated with lower risk of RA [OR_0.35 (0.12–0.97, p_0.04].

Conclusion: In our cohort of patients with early arthritis, the genotypification of HLA-DR alleles was not useful to discriminate between RA and UA. Only the presence of DR15 allele was associated with a lower probability of RA, however the poor precision of the estimates makes it difficult to address the utility of this determination in daily clinical practice.