LETTERS TO THE EDITOR

Debrisoquine oxidation polymorphism in patients with rheumatoid arthritis

The aetiology of rheumatoid arthritis (RA) is unknown. Class II HLA antigens DR4 and DR1 are overrepresented in patients with RA,¹ but other genetic factors may be linked to the susceptibility to the disease. Oxidative polymorphism of debrisoquine (DBQ) is a Mendelian genetic trait modulating the activity of the isozyme CYP2D6 of the cytochrome P450 system. Homo and heterozygotes for a dominant allele are extensive metabolisers (EM) of DBQ and of more than 20 other substrates, whereas those carrying any combination of the various existing recessive alleles are poor metabolisers (PM).² This polymorphism may be related to the risk of having lung, breast and bladder cancers³ and systemic lupus erythematosus.⁴ Environmental factors are involved in the pathogenesis of all these disorders, and perhaps of RA. We have determined the oxidative phenotype of DBQ in a group of patients with RA to show whether this genetic trait is related to the risk of developing the disease.

The study was performed in 78 (23 men, mean age 60.9 years, 95% confidence interval 58.8-63) Spanish patients with RA diagnosed according to the 1987 revised ACR-criteria.⁵ All patients had received second line therapy. No patient had liver and/or kidney disease or had taken drugs known to interfere with the metabolic rate of DBQ⁶ in at least the previous six weeks. The study was approved by the Local Ethical Committee.

The control group was composed of 837 healthy subjects (391 men, mean age 26.3 years, 95% CI 25.6-26.9) not taking any drugs.

The oxidative phenotype of DBQ was determined by giving a 10 mg Declinax tablet at 22:00 hours. Urine of the following eight hours was collected. DBQ and its main metabolite, 4-OH-DBQ, was measured by chromatography⁷ and metabolic ratio (MR = excreted DBQ/excreted 4-OH-DBQ) was calculated. Subjects with MR <12.6 (Log10 <1.1) were classified as EM and those with MR >12.6 were classified as PM of DBQ.⁸ Four patients (5.13%) and 42 controls (5.03%) were PM of DBQ (no significant difference). No differences were observed when comparing MR values by gender. When analysing separately EM subjects of both groups (figure), Log10 of MR values were normally distributed (Kolmogorov-Smirnov test) and were significantly lower ($p < 0.001$, U Mann-Whitney's test) in controls (mean = -0.295, SD = 0.427) than in patients (mean = -0.085, SD = 0.388), indicating a higher hydroxylating ability in the control group.

No relationship exists between oxidative phenotype of DBQ and the risk of developing RA. Nevertheless, the EM phenotype includes two genotypes: homo and heterozygotes for the dominant-functioning wild-type allele. Heterozygotes carry one of the three existing non-functioning mutant recessive alleles, A, B or D.² Homozygote EMs tend to have lower values for MR than heterozygote EMs,²⁻⁹ indicating that they are more efficient oxidisers than heterozygote EMs, suggesting a gene-dose effect. Nevertheless, there is a broad overlap of Log10 of MR values between both EM genotypes (figure) that makes it impossible to classify individually EMs as homo or heterozygous only in the basis of their values for MR.

Our results suggest that there is an excess of heterozygote EMs patients with RA. The mean age in our control group was much lower than in patients, but age does not influence the metabolic rate of DBQ in otherwise healthy subjects.¹⁰ Many patients were taking NSAIDs and/or low dose prednisone when they were phenotyped, but these drugs do not seem to modify the oxidation of DBQ.⁶

We conclude that the possible excess of any recessive-mutant allele(s) of the CYP2D6 gene we have detected among patients with RA should be confirmed by using genotyping procedures to establish which, if any, allele is linked to the risk of RA.

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Frequency distribution of the values for Log10 of metabolic ratio (MR) of debrisoquine in the control group (left) and in RA patients (right). The limit (antimode) between extensive (EM) and poor (PM) metabolisers is fixed at a value for Log10 MR of 1.1. Values in EM patients are higher ($p < 0.001$) than in controls, suggesting an excess of heterozygote EMs in the patients' group.