Host and viral factors in AIDS pathogenesis

Kwa, I.S.

Publication date
2002

chapter|3

Lack of evidence for an association between polymorphism in CX3CR1 and clinical course of HIV infection or virus phenotype evolution

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AIDS, in press

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Summary

A polymorphism in CX3CR1, a coreceptor for some HIV-1 variants, has been associated with a strong acceleration of HIV-1 disease progression. In the Amsterdam Cohort of Homosexual men with HIV and AIDS, we were unable to confirm these findings. In addition, we did not find an effect of this polymorphism on the acquisition of SI/X4 HIV variants.

Genctic polymorphisms in chemokine receptors/ HIV coreceptors have been associated with changes in the clinical course of HIV infection (9) (1,2,2,6,10). The strongest and best confirmed polymorphism is a 32 base pair deletion in the CCR5 gene which has been associated with protection from HIV infection and delayed diseasse progression. Recently, Faure et al. reported that allele M280 of the chemokine receptor CX3CR1 is associated with increased risk for HIV infection and an accelerated clinical course after infection (3). In three French cohort studies (seroconverter cohort, SEROCO; standard progressor cohort (IMMUNOCO) and a long term asymptomatic cohort (ALT), these authors showed a significantly increased relative risk for AIDS associated with M280 homozygosity. Here we report the absence of this association in the Amsterdam Cohort of Homosexual Men with HIV (ACH).

Allele M280 has two non-synonymous single nucleotide polymorphisms (SNPs), causing substitution of isoleucine (I) for valine (V) at codon 249 and methionine (M) for threonine (T) at codon 280. By combining these SNPs, three different alleles can be formed. V249 M280 has never been observed and is therefore considered to be in complete linkage disequilibrium. This allel is refered to as M280. The ACH has been described before (1). Analysis of the CX3CR1 genotype was performed as described by Faure et al (3).

Within the ACH, the distribution of CX3CR1 280 genotypes was not different from previously reported distributions (T/T280, 70.5% (n=241); T/M280, 27.5% (n=94); M/M280, 2% (n=7) (3). Due to the very low frequency of M/M280 homozygotes, we decided to combine the M/M280 group with the T/M280 for further analysis and refer to these groups as M280 allele carriers.

Using a Cox proportional hazards model, progression rates to AIDS and death were not significantly different for M280 allele carriers and T280 homozygotes (Relative Risk (RR) for AIDS: 0.955 [Confidence Interval (CI): 0.701-1.303; p=0.77]; RR for death: 0.978 [CI: 0.703-1.362; p=0.896]. There was also no increased risk for the development of SI/X4 variants (RR 1.196 [CI: 0.753-1.899; p=0.448].

In Kaplan-meier analysis for determining the probability of survival without AIDS-1987, the clinical course of HIV infection in the absence or presence of the M280 allele was not different (Figure 1a, p=0.773). Using death as an end point in Kaplan-meier analysis also did not reveal an influence of the M280 allele on the clinical course of infection (Figure 1b, p=0.896).

Finally, we analyzed whether the acquisition of X4 HIV-1 variants was influenced by the M280 allele. This Kaplan-meier analyses, in which SI conversion as determined by the capacity of patient's HIV-1 variants to replicate in the MT2 cell line, was used as an end point also did not reveal any differences between carriers of the M280 allele and T/T280 homozygotes (Fig. 1c, p=0.448).

Our results contradict the observations by Faure et al in the French cohorts but are in agreement with observations in several North American cohorts (5).

As discussed previously (5), the discrepancy in results could be due to differences in cohort composition. Known differences include gender and HIV risk category. Indeed, the NA cohorts as well as ACH are entirely male, whereas 22% of the participants in the SEROCO cohort are women. With respect to HIV risk category, there are only homosexual men in ACH as compared to heterosexuals and intravenous drug users in SEROCO.

For most chemokine and chemokine receptor polymorphisms different influences on the clinical course of HIV infection have been observed in different cohorts (2,7-9,11,12). To conclude that genetic polymorphisms influence the clinical course of infection in general, meta-analysis studies are definitely required (4). Although the observations in the NA cohorts, the French cohorts and the ACH do not support a clear role for CX3CR1 in AIDS pathogenesis, the underlying mechanism for these discrepancies remains interesting.

Acknowledgement

Financial support for this study was provided by the Netherlands Research Council (NWO, grant no.901-02-214). This study was performed as part of the Amsterdam Cohort Studies, a collaboration between the Academic Medical Center, the Municipal Health Service and Sanquin Research at CLB in Amsterdam, The Netherlands. The Amsterdam Cohort Studies are financially supported by NWO and the Dutch AIDS fund.

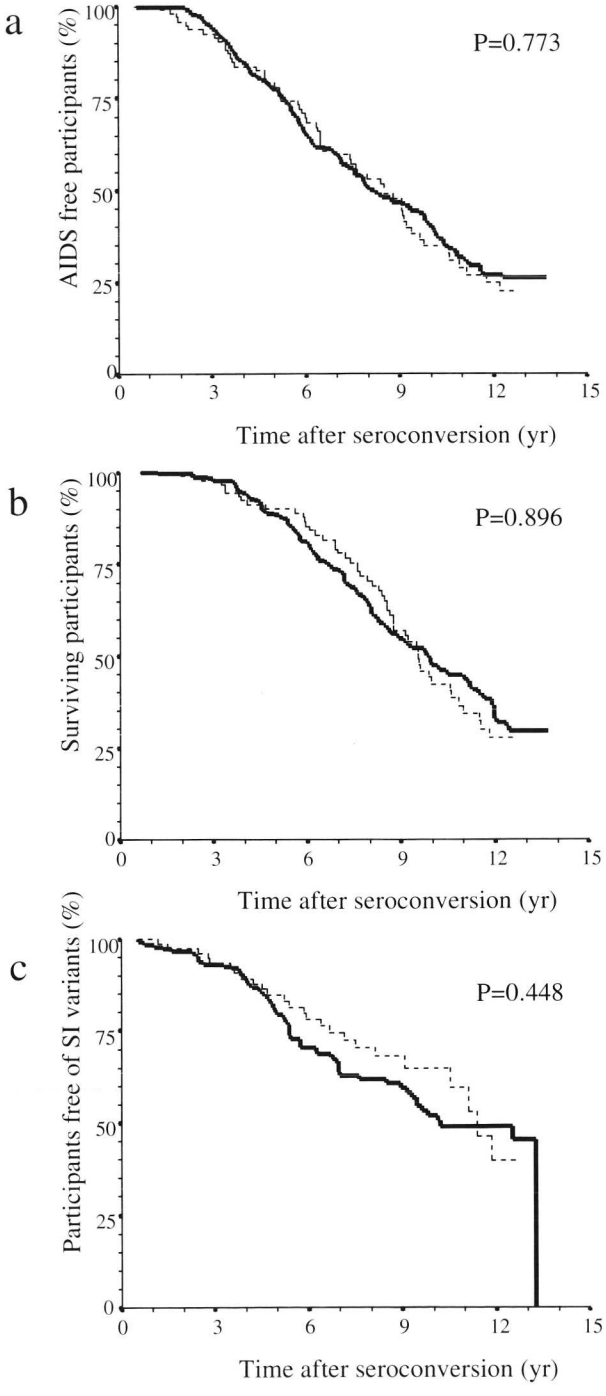

Figure 1. CX3CR1 genotype and HIV-1 disease progression. Kaplan-Meier survival analysis for time in years to AIDS (1987 CDC definition) (A), time in years to death (B) or time in years to acquisition of SI/X4 HIV-1 variants (C). Individuals with the M280 allele are represented by the dashed line, individuals homozygous for the T280 allele are indicated by the solid line. Log-rank P values are shown.

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