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Polymorphisms of Cx3CR1 and CXCR6 receptors in relation to HAART therapy of HIV Type 1 patients

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Abstract
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Polymorphisms of Cx3CR1 and CXCR6 Receptors in Relation to HAART Therapy of HIV Type 1 Patients

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ABSTRACT

The chemokine polymorphisms CXCR6-3K, In1.1T/C, H7 haplotype, CX3CR1-V249I, and CX3CR1-T280M have been shown to affect the course of HIV infection. We studied their influence on immunologic and virologic response to HAART in a group of 143 HIV-1 patients. We performed Kaplan–Meier analysis using the following end-point criteria: (1) time from HAART initiation to undetectable viral load (VL < 50 copies/ml), (2) maximum duration of viral suppression, (3) time from HAART administration until CD4 elevation above 200 cells/μl for patients with baseline CD4 below 200 cells/μl and above 500 cells/μl for patients with baseline CD4 between 200 and 500 cells/μl, respectively, and (4) time from HAART initiation until CD4 reduction below baseline values. Our results revealed an improved immunologic response to HAART in patients with the CX3CR1-249I or CX3CR1-280M allele. On the contrary, patients with initial VL suppression due to HAART showed a faster virologic failure in the presence of the CXCR6-3K allele. The In1.1T/C polymorphism and H7 haplotype did not reveal any specific effect on HAART response.

INTRODUCTION

Many advances have been made in the understanding of HIV infection and treatment. Highly active antiretroviral treatment (HAART) has prolonged survival considerably and reduced the overall HIV-related illnesses. The increasing knowledge of HIV pathogenesis at the molecular level has provided new options for effective treatment.1 The chemokine network is one of the major investigation areas because of its implication in virus-cell entry and immune response mechanisms. The best example to date is the chemokine receptor CCR5, which is the main co-receptor in CD4-mediated cell invasion, particularly in the primary and asymptomatic stage of the infection.2 The chemokine receptor mutant allele CCR5Δ32 generates nonfunctional co-receptor conferring resistance to HIV-1 infection in homozygous individuals and delayed disease progression in heterozygous HIV-1-infected patients.3–8 Genetic variants in the chemokine network that may influence HIV infection are being actively pursued. CXCR6-E3K, In 1.1 T/C (RANTES promoter), haplotype H7 (MCP-1, MCP-3, and eotaxin genes), CX3CR1-V249I, and CX3CR1-T280M are chemokine-associated polymorphisms that have been reported to affect aspects of HIV infection.

RANTES, a ligand for CCR5, competes with HIV-1 in coreceptor usage and may inhibit both cell entry of R5 virus strains9 and viral-mediated activation-induced cell death.10,11 In1.1-T/C is a single nucleotide polymorphism (SNP) in the first intron of the RANTES gene and affects gene transcription through differential binding of nuclear proteins. The In1.1C allele has been associated with rapid progression to AIDS by down-regulating RANTES expression.12

CXCR6 is considered a secondary coreceptor used by all HIV strains. It is expressed in lymphoid tissues, by Th1 and Tc1 lymphocytes and subsets of NK cells, thus making those subpopulations potential targets for HIV-1 infection.13–16 CXCL16, its natural ligand, is produced at various sites,

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particularly during inflammation, rendering the complex CXCR6-CXCL16 important for Th1-Tc1 and NK homing in extralymphoid tissues and sites of inflammation.\textsuperscript{17–19} An SNP designated CXCR6-E3K results in a nonconservative change in codon 3 of the N-terminus of the co-receptor (CXCR6-3K). The CXCR6-3K allele has been related to increased survival from \textit{Pneumocystis carinii} pneumonia (PCP) to death, thereby suggesting reduced susceptibility to \textit{Pneumocystis carinii}.\textsuperscript{20}

The chemokines MCP-1, MCP-3, and eotaxin have been implicated in HIV-1 pathogenesis through chemotaxis and cell activation. MCP-1 has been shown to enhance viral replication in peripheral mononuclear cells\textsuperscript{21} and has been associated with neuronal impairment.\textsuperscript{22–24} On the other hand, MCP-3 is a physical antagonist of CCR5\textsuperscript{25} and has been shown to inhibit HIV-1 replication.\textsuperscript{26} Their genes are adjacent and located on the long arm of chromosome 17, including nine known SNPs, which present specific haplotypes. Among these haplotypes, H7 is defined by the combination of three alleles, at codons 2136, 767, and 1385 (MCP-1 promoter-2136T, MCP-1 767G, and eotaxin promoter 1385A), and occurs at a significantly higher frequency in multiply exposed, noninfected individuals in comparison with seroconverters, suggesting a protective role of this haplotype on HIV-1 infection.\textsuperscript{27}

CX3CR1 is a receptor for the chemokine fractalkine and is expressed on monocytes, lymphocytes, and neutrophils and abundantly on glial cells and astrocytes. Fractalkine and CX3CR1 seem to play an important role in HIV-1-associated dementia, immune cell recruitment, and possibly in infection expansion by acting as co-receptors in viral entry.\textsuperscript{28–30} CX3CR1-V249I and CX3CR1-T280M are SNPs of the receptor. Their role in HIV infection is not clear. It has been argued that they exhibit a deleterious effect on the progression to AIDS,\textsuperscript{31–33} although protective or insignificant effects on HIV progression have also been reported.\textsuperscript{31,34}

All the above polymorphism effects have been studied principally in established cohorts of untreated patients. Furthermore, their influence has been evaluated mostly by using survival analysis in relation to clinical progression or death end-points. After the introduction of HAART, the clinical course of HIV-1 patients has changed dramatically by increasing survival and reducing HIV-1-related illnesses, making death and illness-defined staging less suitable for polymorphism evaluation. Additionally, HAART alters viral activity and affects immune processes. The contribution of chemokine polymorphisms in response to HAART probably differs from that in untreated patients. We have previously applied immunologic and virologic markers [CD4+ T cells, viral load (VL)] to assess the impact of four chemokine-associated polymorphisms on the effectiveness of HAART.\textsuperscript{35} We established a significantly protective effect of CXCL12-3A’ and CCR2-64I on immunologic and virologic responses, respectively, whereas the CCR5Δ32 and promoter CCR5-59029G/A polymorphisms had no effect. In the present study, we investigated the contribution of five chemokine polymorphisms, CXCR6-E3K, In 1.1 T/C, promEotaxin-1385G/A (haplotype H7), CX3CR1-V249I, and CX3CR1-T280M, in relation to immunologic and virologic responses to HAART.

**MATERIALS AND METHODS**

**Patients**

“A. Syngros” Hospital is one the major HIV treatment centers in Greece. We studied retrospectively a group of 143 patients (123 males and 20 females) treated with HAART and followed up by the HIV department of this hospital. The mean age at the time of diagnosis was 41.2 (range 23–77) years. Fifty patients were therapy experienced, with regimens consisting of one or two nucleoside reverse transcriptase inhibitors (NRTI). On HAART initiation, 44 experienced patients were switched to a 2 NRTI + PI regimen (PI: protease inhibitor) and 6 patients were switched to a 2 NRTI + NNRTI regimen (NNRTI: nonnucleoside reverse transcriptase inhibitor). All new drug combinations included at least one NRTI agent the patient had not been previously exposed to in combination with a PI or an NNRTI. Among the therapy-naïve patients, 71 started HAART with a 2 NRTI + PI regimen and 22 with a 2 NRTI + NNRTI regimen. The mean follow-up duration after HAART initiation was 68.8 (11–109) months. Monitoring of patients’ CD4 and HIV VL was performed according to standard guidelines.\textsuperscript{36} Ethical approval was obtained from the local ethics board of the “Syngros” Hospital. The medical records and the genotyping results had anonymous codes.

**CD4 T cell count and viral load estimation**

HIV-1 RNA levels were measured in blood plasma using RNA amplification assays (NucliSENS-NASBA Diagnostics). CD4 T cell counts were performed by four-color flow cytometry using monoclonal antibodies from Becton Dickinson (San Jose, CA).

**Blood collection, DNA extraction, and genotyping**

Peripheral blood was collected from patients, stored, and processed for DNA extraction as previously described.\textsuperscript{35} The presence of amplifiable DNA was confirmed in all specimens. Genotyping was performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. Two negative controls were used for each PCR reaction to exclude contamination. The primers used for the genetic analysis are presented in Table 1.

The PCR and RFLP conditions for each SNP were the following: (1) For RANTES-In1.1T/C: denaturation at 94°C for 3 min, 35 cycles of denaturation at 92°C, annealing at 54°C, extension at 72°C for 30 sec each, and final extension at 72°C for 10 min. The PCR product (342 bp) was incubated for 1 h at 37°C by \textit{MboII} and in the presence of In1.1C cut into two fragments (219 bp + 123 bp). (2) For CXCR6-E3K the same conditions were used apart from the annealing temperature (51°C). The PCR product (145 bp) was incubated at 37°C for 3 h by \textit{HindIII} and produced two fragments (121 bp + 24 bp) when the 3K variant was present. (3) For haplotype H7 we detected the variant 1385A in the promoter of eotaxin. According to Modi \textit{et al.},\textsuperscript{27} haplotype H7 is defined by the unique combination of three variants, 2136T (MCP-1 promoter), 767T (MCP-1 coding region), and 1385A (eotaxin promoter). In this combination, the frequency of promEotaxin-1385A (0.193) corresponds closely to the frequency of the H7 haplotype.
Therefore by genotyping the patients for promEotaxin-1385A, we obtained an accurate estimate of haplotype H7 presence. The PCR conditions for promEotaxin-1385A were the same as for CXCR6-E3K, and the PCR product was 279 bp. The 1385G variant creates an MspI restriction site, and two fragments (153 bp/126 bp) are produced after incubation at 37°C for 4 h. (4) For CX3CR1-V249I and CX3CR1-T280M, the PCR conditions were denaturation 3 min at 94°C and 35 cycles of 30 sec denaturation at 94°C, 40 sec annealing at 50°C and 55 sec extension at 72°C, followed by 10 min final extension at 72°C. After digestion by AclI (37°C, 3 h) the 249V variant splits into two fragments (205 bp/383 bp), whereas the 249I variant remains undigested (588 bp). Additionally, after digestion by BsmBI (55°C, 3 h), the 280T and 280M alleles are cut into three fragments (75, 216, and 297 bp), and two fragments (216 and 372 bp), respectively. All products were visualized on 2% agarose gel electrophoresis (with the exception of CXCR6-E3K polymorphism products, for which a 3% agarose gel was used) after ethidium bromide staining. To confirm the digestive efficiency of each restrictive enzyme, we used plasmid DNA containing the equivalent restriction site as a positive control in each digestion.

### Statistical analysis

We defined baseline CD4 and baseline VL (time = 0) from the most recent measurements prior to HAART initiation (range: 1–4 months prior to therapy). Using baseline CD4 we
defined three groups according to CDC criteria for CD4 staging. The first, second, and third category included patients with baseline CD4 ≥500, 200–499, and <200 cells/mm³, respectively. We performed Kaplan–Meier analysis using four endpoints: (1) Virologic success, defined as the time from HAART initiation to the first VL count below the detectable threshold (50 cps/mm³). (2) Virologic failure, defined as the time from the first undetectable VL to the second consecutive VL count above 50 cps/mm³. We used two consecutive VL counts above 50 cps/mm³ in a 1–3 month interval as a definition for virologic failure in order to avoid bias from viral blips. (3) Immunologic success, defined as the time from HAART to the first CD4 measurement that exceeds the next CD4 category (if baseline CD4 <200, time until first CD4 ≥200; if baseline CD4 is 200–499, time until first CD4 ≥500). (4) Immunologic failure, defined as time from HAART initiation until the second continuous CD4 measurement, which fell below baseline level.

Patients who did not manage to reach the end-point were censored on the date of last CD or VL measurement. Five patients who did not suppress VL to undetectable levels were excluded from the virologic failure analysis (second end-point). One therapy experienced patient had baseline VL <50 and was excluded from analysis of VL success (first end-point). The patients who had baseline CD4 ≥500 (see Table 1) were excluded from the analysis of immunologic success (third end-point). Statistical significance was estimated by the log rank test. Analysis was performed using SPSS software (edition 11.0 for Windows).

RESULTS

Genotyping analysis was performed on 143 patients for the variants RANTES-In1.1T/C, CXCR6-E3K, promEotaxin-1385G/A, CX3CR-V249I, and T280M. The results are presented in Table 1. The allele frequency for each polymorphism was 0.028 for CXCR6-3K, 0.127 for In1.1C, 0.196 for promEotaxin-1385A, 0.258 for CX3CR1-V249I, and 0.157 for CX3CR1-280M. The CX3CR1-V249I and CX3CR1-T280M polymorphisms were in linkage disequilibrium and CX3CR1-280M was never found on the same haplotype with CX3CR1-V249I. Although CX3CR1-V249I was found with CX3CR1-280T, because of the small allele frequency of CXCR6-3K, we examined the effect on HAART response associated with the presence of the -3K allele versus the homozygous wild type.

Regarding the end-point, defined as the time from HAART initiation until CD4 exceeds the next category (if CD4 <200, the time until CD4 ≥200 but <500, if CD4 200–499 the time until CD4 ≥500), we found that the presence of the 249I and 280M allele was associated with a rapid CD4 elevation, predominantly in homozygous states (mean 3 ± 1, 3 ± 2 for 249I and 280M/Vs and 16 ± 2, 19 ± 3 in homozygous wild types, respectively). This association was statistically significant (p = 0.0014 for V249I and p = 0.0241 for T280M) (Fig. 1A and B, respectively). The remaining polymorphisms showed no such effect on immunologic response to HAART initiation.

Regarding the end-point, defined as the time from the first VL <50 cps/mm³ until the second VL >50 cps/mm³, we found a significant association between the CXCR6-3K and faster VL recurrence. Patients bearing CXCR6-3K allele showed faster detectable viremia than those homozygous for the common CXCR6-3E allele (mean 19 ± 6 and 48 ± 3 months, respectively, p = 0.0359, n = 137) (Fig. 1C). On the contrary, In1.1T/C, promEotaxin-1385G/A, CX3CR1-V249I, and CX3CR1-T280M polymorphisms showed no such correlation.

Regarding the two end-points, defined as the time from HAART initiation until the first VL below 50 cps/mm³, and the time from HAART initiation until CD4 fell under baseline, we found no significant correlation between the polymorphism genotypes and virologic success or immunologic failure, respectively.

Additionally we used the same end-points to compare HAART response between therapy-naïve and therapy-experienced patients. We found that therapy-naïve patients reached undetectable VL levels faster (p = 0.023, mean time for naive and experienced patients was 11 ± 2 and 18 ± 3 months respectively), sustained undetectable VL longer (p = 0.003, mean time for naive and experienced patients 53 ± 4 and 33 ± 4 months, respectively), and increased CD4 counts faster (p = 0.033, mean time for naive 13 ± 2 and for experienced patients 23 ± 4 months) than therapy-experienced patients. On the contrary, we compared patients receiving 2 NRTI + PI with patients receiving 2 NRTI + NNRTI regimens using the same end-points and found no significant difference in HAART response (data not shown). Unfortunately, performing Kaplan–Meier analysis for the chemokine polymorphisms using the patient subgroups as strata (therapy naïve vs. experienced or 2 NRTI + PI vs. 2 NRTI + NNRTI) resulted in small subgroups with small statistical power due to the small initial sample size.

DISCUSSION

In the present study, we retrospectively investigated the impact of five chemokine polymorphisms on the immunologic and virologic response to HAART of a group of 143 patients. We observed that patients bearing the CXCR6-3K variant could not sustain undetectable VL as long as the common variant, whereas CXCR1-249I and CXCR1-280M correlated with faster CD4 escalation. Additionally, the In1.1 and promotor eotaxin 1385G/A polymorphisms were not found to affect CD4 or VL response to HAART.

The presence of the CXCR6-3K allele was associated with impaired viral suppression after HAART in our study. The mean duration of undetectable VL was 48 ± 3 in CXCR6-3E homozygous patients (n = 131) and only 19 ± 6 in patients heterozygous or homozygous for the CXCR6-3K allele (n = 6). This effect was significant (p = 0.0359), and it is the first time, to our knowledge, that it has been reported in relation to HAART. The remaining three end-points were not affected by the CXCR6-3K allele. Duggal et al.,20 on the contrary, reported a protective effect of the CXCR6-3K allele on the time from PCP to death in a group of 60 African-American (AA) HIV-1 patients who died from PCP and did not receive HAART. The nonconservative Glu-to-Lys change in the extracellular domain of the receptor may well affect CXCR6 function as coreceptor for HIV-1 (permitting expansion of HIV-1-infected cells) or affect the CXCR6-related response of Th1, Tc1, and NK cells to signaling pathways induced by CXCL16, thus altering immune
reactions to HIV-1 infection. In our group of patients, the frequency of CXCR6-3K was found to be 2.8% and demonstrated a deviation from the Hardy–Weinberg equilibrium \((p < 0.001, E/K = 8, \text{expected } K = 1)\). In contrast with our study, Duggal et al.\(^2\) found the allelic frequency of CXCR6-3K to be 44% in a cohort of 805 AA, with no HW disequilibrium deviation, and less than 1% in EA, without mentioning HW tests in EA. The deviation observed could be attributed to the small allele frequency and random selection. Alternatively, the small number of heterozygotes may reflect the negative impact of the -3K allele on the course of infection.

The CX3CR1-V249I and CX3CR1-T280M variants, in our study were associated with a favorable effect on HAART response in comparison to the CX3CR1-C249V and CX3CR1-C280T alleles, respectively. The effect was more profound in the homozygous states. The mean time from HAART initiation to CD4 escalation above the next CDC category was 3 ± 1 months for CX3CR1-C249I/I and 3 ± 2 months for CX3CR1-C280M/M (or homozygous 280M haplotype) versus 16 ± 2 for CX3CR1-C249V/V and 19 ± 3 for CX3CR1-C280T/T \((p = 0.0014, p = 0.0241, \text{respectively})\). In contrast, no correlation was observed between the allele genotypes and virologic success or virologic and immunologic failure. Additionally, our findings on allele frequencies \((f(249I) = 0.258, f(280M) = 0.157)\) and linkage disequilibrium between the CX3CR1-249I and CX3CR1-280M variants are in agreement with previous reports.\(^3\)\(^1\)\(^2\)\(^3\) The role of these polymorphisms is still under debate. Faure et al.\(^2\)\(^8\)\(^,\)\(^3\)\(^1\) repeatedly reported a deleterious effect of the homozygous CX3CR1-280M state on disease progression to AIDS in cohorts of untreated patients. Brumme et al.\(^3\)\(^3\) studied the immunologic and virologic response to HAART in a group of 461 treatment-naïve patients showing a higher rate of immunologic failure (defined as CD4 reduction below baseline levels) in the homozygous CX3CR1-249I patients. A faster progression to AIDS...
in association with the CX3CR1-249I allele was also reported by Singh et al. in a cohort of HIV-1-infected children receiving non-HAART regimens. On the contrary, McDermott et al. reported a slightly delayed progression to AIDS and all cause death in untreated patients bearing the CX3CR1-280M haplotype. This was considered to be consistent with reduced activity of the mutant receptor in comparison with the wild-type receptor, as demonstrated in HIV fusion assays. Although Kwa et al. found no correlation between the CX3CR1-249I280M haplotype and progression to AIDS or death, Vidal et al. found an increased frequency of CX3CR1 249I in long-term nonprogressors, suggesting a protective effect by the -249I variant. Interestingly, in our group of patients, the correlation between 249I and improved CD4 restoration exhibited a higher significance (p = 0.0014) than 280M (p = 0.0241). Indeed, rapid CD4 escalation was observed even in patients with 249I and without 280M. On the contrary, the effect of 280M alone could not be demonstrated because all 280M haplotypes contain 249I. This suggests that the protective effect of the tightly linked CX3CR1-249I280M haplotype is mainly attributed to the 249I variant.

We genotyped our patients for the 1385G/A polymorphism in the eotaxin promoter region and found a frequency of 19.6% for the 1385A allele, which is in agreement with a previously reported frequency. Although 1385A is one of three variants characteristic of H7 (the other two being 2136T and 767G), we considered it alone to represent the frequency of H7 accurately, because among the eight haplotypes (H1–H8) described, 1385A is found only on H7 with an almost identical allele and haplotype frequency (0.193 for 1385A and 0.192 for H7). In the statistical analysis that followed, no significant correlation was established between the promEotaxin-1385G/A polymorphism and any of the selected end-points, and therefore haplotype H7 was not shown to have any profound effect on the immunologic and virologic markers of HAART success. In contrast, Modi et al. reported the increased presence of H7 in highly exposed uninfected individuals, implicating it in resistance to infection. Similarly, we found In1.1C at a frequency of 12.7%, in agreement with the frequency reported previously. Additionally, the In1.1T/C polymorphism did not exhibit any significant correlation with HAART response with respect to the four end-points employed. According to An et al., the In1.1C variant is located in an expression-regulating element (intron 1) of the RANTES gene and results in down-regulation of RANTES transcription through differential binding of nuclear proteins. This resulted in accelerated progress to AIDS in cohorts of untreated patients. We did not find similar effects in relation to HAART. However, our study is only the first report on the impact of H7 haplotype and In1.1C/T on the treatment of HIV-1 infection and our findings await confirmation from larger cohorts.

The present study was performed exclusively in Caucasians and our observations may be restricted to equivalent populations. It must be noted, also, that certain limitations apply to our results. All treatments applied were in accordance with recommended guidelines for maximal viral suppression. We examined the possibility of bias due to different antiviral treatment and compared patients treated with 2 NRTI + PI versus patients with 2 NRTI + NNRTI using the same end-points applied above but found no significant difference between the two groups. Still, bias due to different regimen components and suboptimal patient compliance with therapy cannot be excluded. Additionally, therapy-naive patients revealed improved outcomes in comparison to therapy-experienced patients. Unfortunately, separate Kaplan–Meier analysis of the two patient groups (therapy naïve–experienced) for the chemokine polymorphisms resulted in small subgroups with small statistical power due to the small initial sample size. Studies with larger patient samples are needed to confirm our findings.

In conclusion, we studied the effect of five chemokine polymorphisms previously reported to affect HIV-1 disease progression on the response to HAART initiation in a group of 143 patients with prolonged follow-up. Using Kaplan–Meier analysis, we found that the CXCR6-3K allele correlated with a shorter duration of viral suppression. The CX3CR1-280M and CX3CR1-249I variants were shown to confer improved immunologic response, in terms of faster initial CD4 elevation. No correlations were observed between HAART response and the In1.1T/C or the eotaxin promoter 1385G/A (haplotype H7) polymorphisms. Our results may provide useful information on the role of polymorphisms in the chemokine network and their implications in HIV pathogenesis, particularly during HAART treatment.

REFERENCES


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