# Viral Clearance in Hepatitis C (1b) Infection: Relationship With Human Leukocyte Antigen Class II in a Homogeneous Population

LIAM J. FANNING, JOHN LEVIS, ELIZABETH KENNY-WALSH, FREDA WYNNE, MICHAEL WHELTON, AND FERGUS SHANAHAN

The aim of this study was to investigate the possibility of a significant relationship between human leukocyte antigen (HLA) class II and the clearance of hepatitis C virus (HCV). The study group consisted of 156 Irish women who iatrogenically received HCV 1b–contaminated Anti-D immunoglobulin between May 1977 and November 1978. Thus, the study population was homogeneous in terms of gender, source of infection, and ethnicity. On Screening in 1994, all individuals were anti-HCV antibody positive by recombinant immunoblot assay, while 46% (n = 72) of the group were HCV-positive by reverse transcriptase-polymerase chain reaction (RT-PCR). HLA DRB1 and DQB1 status was molecularly defined by high resolution reverse line probe hybridization methodology. Clearance of HCV 1b was found to be associated with DRB1*01. However, this association was lost after Bonferroni correction for multiple comparisons. Extended haplotype analysis between specific DRB1 and DQB1 allelic combinations identified a significant reduction in the frequency of DQB1*0501 in the presence of DRB1*0701 in the persistently infected individuals in the study group ($P < .05$). No associations with either viral clearance or persistence were found at the DQB1 locus. Our results suggest that HLA DRB1*01 appears to contribute to the spontaneous resolution of a primary HCV infection in the Irish population. The presence of DRB1*0701 in the absence of DQB1*0501 possibly reflects an influence of this allele in persistence of HCV infection. Defined and homogeneous patient populations offer the best opportunity to illuminate previously disguised immunogenetic factors important in the clearance of HCV 1b. (HEPATOLOGY 2000;31: 1334-1337.)

Hepatitis C virus (HCV) infection is the main cause of non-A, non-B hepatitis.[1-5] HCV consists of a heterogeneous mix of isolates defined by genotype, each of which is further classified into subtypes.[6,7] A number of factors have been considered in terms of their potential to predict the outcome of the disease. These include age of infection, viral type-subtype, quasispecies, viral load, and mode of infection.[8-13] Clinical heterogeneity in disease progression may reflect viral heterogeneity and variations in host response.[14-17] The human leukocyte antigen (HLA) has been shown to influence host response to infection.[18-22] Although HLA class II genes have shown associations with viral clearance or persistence of the HCV these findings are not uniform.[23-28] In addition, direct comparisons between studies is often difficult because of heterogeneity of ethnic background, viral genotype, phenotype frequencies of individual alleles between populations, gender, and duration of disease. To avoid heterogeneity of risk factors and confounding variables in viral type/subtype we studied a unique cohort of individuals all infected by anti-D contaminated from a single source of HCV 1b. The patients were of similar ethnogeographic background and had an absence of competing risk factors for liver disease.

The present study is a follow-up investigation of the well-documented series of Irish women who were inadvertently infected with HCV as a result of receiving contaminated anti-D immunoglobulin (from a single source) in 1977 to 1978.[29-31] The contaminating HCV 1b was derived from a single infected donor.[30-33] The homogeneity of this group allows one to examine variation in host response to HCV infection without the potentially confounding influence of factors such as gender, specific HCV genotype, age range, and general health status. The purpose of the present study was to address whether particular HLA class II alleles are associated with clearance or persistence of HCV type 1b.

## PATIENTS AND METHODS

The study group consisted of 156 female individuals all of whom were iatrogenically infected between May 1977 and November 1978 with HCV type 1b from a single source. All 156 cases tested positive for antibodies to HCV (by recombinant immunoblot assay; Chiron Corporation, Emeryville, CA) and 46% (n = 72) were positive for HCV RNA by qualitative reverse transcriptase-polymerase chain reaction (RT-PCR) using the Roche AMPLICOR test (F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland). The HCV status of the 84 patients who tested negative on initial qualitative HCV RT-PCR screening was confirmed by retesting within an 18-month period. The HCV genotype of the 72 virus-positive individuals was confirmed to be HCV 1b by reverse line probe assay (Inno-Lipa HCV II, INNOGENETICS N.V., Zwijndrecht, Belgium).

Investigations were performed with informed consent and complied with a standardized protocol in compliance with standard of care and in accordance hospital ethical guidelines. A detailed history was taken from each individual for assessment of parenteral risk factors for liver diseases such as surgery (53%, n = 84), blood or blood product (7%, n = 11), ear piercing (46%, n = 72/156), tattooing (0.7%, n = 1/156), previous or continuing intravenous drug abuse (none), occupational health exposure (none), sexual or household contact with a person who had hepatitis (none), and

Abbreviations: HCV, hepatitis C virus; HLA, human leukocyte antigen; RT-PCR, reverse transcriptase-polymerase chain reaction.

From the Hepatitis C Unit, Department of Medicine, National University of Ireland, Cork, University College Cork, Cork, Ireland.

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Address reprint requests to: Liam J. Fanning, Ph.D., Hepatitis C Unit, Department of Medicine, Clinical Sciences Building, Cork University Hospital, University College Cork, Cork, Ireland. E-mail: L.FANNING@UCC.IE; fax: (353) 21-345300.



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organ transplant (none). Only in the case of anti-D immunoglobulin was there substantiated evidence for transmission of HCV 1b. All patients tested serologically negative for hepatitis A and hepatitis B (Abbott Laboratories, Laurinburg, NC). None of the patients had received antiviral treatment at the time of study.

*HLA Class II Allelic Identification.* HLA DRB1 (Roche Amplicor HLA DRB1 typing kit; Roche Diagnostic Systems, Branchburg, NJ) and HLA DQB1 status (Innogenetics DQB1B amplification and detection kit; INNOGENETICS N.V.) were molecularly defined by reverse line probe hybridization. The chromosomal DNA used for the HLA DQB1 genotyping was prepared from peripheral blood mononuclear cells using the Wizard genomic DNA purification kit (Promega, Madison, WI).

A total of 12 distinguishable allelic groups consisting of 78 distinct alleles were tested at the DRB1 locus, while 5 distinguishable allelic groups consisting of 26 alleles were tested at the DQB1 locus. Typing to the level of allelic splits was not always possible for each individual. This was because of the presence of two confounding specificities at a locus.

The DRB1 genotyping assay used for this study did not directly distinguish DRB1*15 and DRB1*16 alleles. However, known linkage disequilibrium associations in Caucasian populations between DRB1 and the DRB5 locus can be used to infer the likely DRB1 allele. However, for the purposes of likely allelic associations with viral persistence or clearance, this discrimination was not made because of lack of definitive resolution by the reverse line probe assay. Instead these allelic groups were collated into one group (DRB1*15/*16). DRB1*0701 is the only allelic member of the DRB1*07 allelic group, hence, referred to by the allelic group nomenclature.

*Statistical Analysis.* The $\chi^2$ and Fisher's exact tests were used to compare allele frequencies between persistence and clearance groups. Probability levels were based on two-sided testing, and were considered to be statistically significant where $P < .05$. Where appropriate, $P$ values were corrected using the Bonferroni method taking into account the total number of alleles tested. The statistical software facility used was SPSS for Windows.

## RESULTS

The genotype of HCV was confirmed as type 1b for all the HCV-RNA–positive individuals in the study.

It was not possible to definitively establish the identity of at least one DRB1 allele for 24 (15%) of the combined groups. Similarly, 11 (7%) of the cases were missing data for at least one allele at the DQB1 locus. There was no evidence of either a statistically significant intergroup difference in terms of missing data (Table 1), or any discordance in terms of allele identity in those cases with single gene discernment.

The most frequent alleles were DRB1*07, *03, *15, *04, and *01, each being present for between a fifth and a third of cases in both groups (Table 2). The only statistically significant difference between the groups is seen for DRB1*01 in which a positive association with HCV clearance is suggested; only 6 (9%) of the persistence cohort had this allele compared with 15 (22%) of clearances ($P < .05$). However, after correction for multiple comparisons this difference no longer remained significant (Table 2).

When the DQB1* allele distributions for the persistence and clearance groups are compared a relatively small number of alleles dominate: DQB1*0201, -02, *0301, *0501, and *0601 and -11. However, there was no evidence of a significant intergroup difference for any allele at this locus (Table 3).

The extent and nature of homozygosity was examined for alleles at both the DRB1* and DQB1* loci. In this regard, the most frequent alleles were DRB1*04, DRB1*07, DQB1*0201 and -02, and DQB1*0301. However, there was no statistically significant evidence that specific homozygous expression influences HCV clearance (Table 4).

The data were further explored for evidence of a possible interactive association between (1) specific DRB1* and DQB1* allele combinations, and (2) outcome of HCV infection (Table 5). Initially, the possibility of an association

TABLE 1. Distribution of Confounding Heterozygosity at DRB1 and DQB1 Loci

| Locus Group | Both Alleles Available | 1 Allele Confounding | 2 Alleles Confounding | Significance |
|---|---|---|---|---|
| DRB1 persistent | 64 (89%) | 7 (10%) | 1 (1%) | — |
| Clearance | 68 (81%) | 15 (18%) | 1 (1%) | $P = .35$ |
| DQB1 persistent | 67 (93%) | 5 (7%) | — | — |
| Clearance | 78 (93%) | 3 (3.5%) | 3 (3.5%) | $P = .18$ |

NOTE. DRB1 and DQB1 alleles were defined as molecular by reverse line probe hybridization methodology coupled with a PCR strategy. Confounding heterozygosity was observed at both loci.

TABLE 2. Comparison of DRB1 Allele Distributions Between the Persistence and Clearance Groups

| DRB1* Allele | Clearance N (%) | Persistence N (%) | Significance | Odds Ratio (95% Confidence Interval) |
|---|---|---|---|---|
| 07 | 19 (30%) | 20 (29%) | NS | 1.01 (0.48 to 2.14) |
| 03 | 17 (27%) | 20 (29%) | NS | 0.87 (0.41 to 1.86) |
| 15 | 19 (30%) | 17 (25%) | NS | 1.27 (0.59 to 2.73) |
| 04 | 19 (30%) | 15 (22%) | NS | 1.49 (0.68 to 3.27) |
| 01 | 6 (9%) | 15 (22%) | $P < .05$ | 0.37 (0.13 to 1.01) |
| 13 | 9 (14%) | 10 (15%) | NS | 0.95 (0.36 to 2.51) |
| 0103 | 8 (13%) | 4 (6%) | NS | 2.29 (0.65 to 8.00) |
| 11 | 4 (6%) | 4 (6%) | NS | 1.07 (0.26 to 4.46) |
| 14 | 3 (5%) | 2 (3%) | NS | 1.62 (0.26 to 10.04) |
| 02 | — | 3 (4%) | NS | — |
| 08 | 2 (3%) | 2 (3%) | NS | 1.06 (0.15 to 7.79) |
| 12 | 1 (2%) | 2 (3%) | NS | 0.52 (0.05 to 5.92) |
| 09 | — | 2 (3%) | NS | — |
| 10 | 1 (2%) | — | NS | — |

NOTE. Statistically significant results are in bold.
Abbreviation: NS, not significant.

TABLE 3. Comparison of DQB1 Allelic Distributions Between the Persistence and Clearance Groups

| DQB1* Allele | Clearance N (%) | Persistence N (%) | Significance | Odds Ratio (95% Confidence Interval) |
|---|---|---|---|---|
| 0201,-02 | 26 (39%) | 37 (47%) | NS | 0.70 (0.36 to 1.36) |
| 0301 | 18 (27%) | 25 (32%) | NS | 0.78 (0.38 to 1.60) |
| 0501 | 16 (24%) | 20 (26%) | NS | 0.91 (0.43 to 1.94) |
| 0602,-11 | 15 (22%) | 19 (24%) | NS | 0.90 (0.41 to 1.94) |
| 03032,-06 | 8 (12%) | 9 (12%) | NS | 1.04 (0.38 to 2.87) |
| 0302,-07 | 7 (10%) | 6 (8%) | NS | 1.40 (0.45 to 4.39) |
| 0603 | 3 (5%) | 5 (6%) | NS | 0.68 (0.16 to 2.98) |
| 05031 | 3 (5%) | 1 (1%) | NS | 3.61 (0.37 to 35.55) |
| 0604 | 1 (2%) | 3 (4%) | NS | 0.38 (0.04 to 3.73) |
| 0402 | 2 (3%) | 1 (1%) | NS | 2.37 (0.21 to 26.73) |
| 0502 | — | 1 (1%) | NS | — |
| 0305 | — | 1 (1%) | NS | — |
| 0304 | — | 1 (1%) | NS | — |
| 06051 | 1 (2%) | — | NS | — |
| 0609 | — | 1 (1%) | NS | — |

Abbreviation: NS, not significant.

TABLE 4. Extent of Homozygosity at Both the DRB1* and DQB1* Loci

| | Persistence | Clearance | Significance |
|---|---|---|---|
| DRB1* Allele | | | |
| 04 | 1 (2%) | 6 (9%) | NS |
| 07 | 5 (8%) | 2 (3%) | NS |
| 15 | 4 (6%) | — | NS |
| 03 | — | 1 (2%) | NS |
| 02 | — | 1 (2%) | NS |
| DQB1* Allele | | | |
| 0201,-02 | 9 (13%) | 6 (8%) | NS |
| 0301 | 3 (5%) | 4 (5%) | NS |
| 0602,-11 | 4 (6%) | 1 (1%) | NS |
| 03032,-06 | — | 1 (1%) | NS |
| 0302,-07 | — | 1 (1%) | NS |
| 05031 | 1 (2%) | — | NS |

Abbreviation: NS, not significant.

between each of the 5 most common alleles at both loci was examined. In each case where the relationship was statistically significant ($P < .05$), the precise nature of the association was noted separately for the persistence and clearance groups (Table 5). A number of strong links are evident, including (1) the almost universal presence of DQB1*0602 and -11 with the expression of DRB1*15, (2) a similar association between DRB1*01 and DQB1*0501, and (3) a substantial decrease in DQB1*0301 expression when DRB1*01 is present. In general, these relationships are independent of HCV clearance status. However, the reduced frequency of DQB1*0501 in the presence of DRB1*07 is more pronounced in the persistently infected group ($P < .05$) (Table 5).

## DISCUSSION

A difficulty that lends itself to lack of clarity in identification of those HLA alleles that are associated with HCV persistence or clearance is that many of the studies to date report associations between clearance or persistence based on comparison of patient populations and controls from the normal population.[24-27] We have circumvented this by comparing HLA frequencies between patients who have persistent viremia and those who have evidence of past infection but effected viral clearance, and where all of the individuals were exposed to HCV 1b from the same source. An additional advantage to investigating which immunogenetic elements are important in the immune response to HCV in a single source outbreak of iatrogenic HCV infection, is that these elements are more easily detected in patient cohorts with similar ethnogeograhphic backgrounds. Diversity of ethnic composition and viral genotype may obscure these data.

TABLE 5. Interactive Association Between the 5 Most Common DRB1* Allelic Groups and the 5 Most Frequent DQB1* Alleles Within the Persistence and Clearance Groups

| DRB1* Allele | Specific DQB1* Allele | Status | Persistence | Clearance |
|---|---|---|---|---|
| 04 | 0301 | Absent | 4/40 (10%) | 10/51 (20%) |
| | | Present | 11/19 (58%) | 10/13 (77%) |
| 07 | 0201,-02 | Absent | 13/40 (33%) | 16/44 (36%) |
| | | Present | 10/19 (53%) | 13/20 (65%) |
| 07 | 0501 | Absent | 15/40 (38%) | 14/44 (32%) |
| | | Present | 0/19 (0%) | 4/20 (20%) |
| 15 | 0602,-11 | Absent | 0/44 (0%) | 5/48 (10%) |
| | | Present | 15/15 (100%) | 14/16 (88%) |
| 03 | 0201,-02 | Absent | 13/43 (30%) | 13/45 (29%) |
| | | Present | 10/16 (63%) | 16/19 (84%) |
| 03 | 0301 | Absent | 15/43 (35%) | 19/45 (42%) |
| | | Present | 0/16 (0%) | 1/19 (5%) |
| 01 | 0501 | Absent | 9/53 (17%) | 5/50 (10%) |
| | | Present | 6/6 (100%) | 13/14 (93%) |

NOTE. $P < .05$ highlighted in bold.

Our findings of a weak association between clearance of HCV 1b and DRB1*01 is in agreement with the recently reported associations between the HLA DRB1*01 allelic group and HCV clearance.[28] This confirmation of an association of the DRB1*01 allelic group with clearance of HCV adds further credence to the hypothesis that this allelic family contains important immunogenetic factor(s) that assist in the resolution of primary HCV 1b infection. However, it is interesting to note that a recent investigation of potential HLA class II associations with outcome of HCV infection, did not find any association between DRB1*0101 and clearance. It is possible that the association between the DRB1*01 allelic group and clearance of HCV infection is particular to the Irish population.

Association between DQB1*0401 and HCV persistence has been observed in the Japanese population.[24] We did not detect statistically significant associations between persistent infection and the DQB1*0401 allele. However, this may be explained by accounting for differences in the phenotype frequency (pf) of DQB1*0401 alleles in the Japanese and Irish populations, where n is equal to the number of subjects possessing the particular phenotype, and P is equal to the total number of subjects in the sample population; (pf = n/P); pf(Japan) = 0.28, n = 260, P = 916, and pf(Ireland) = 0, n = 0, P = 93. Tibbs et al.[34] reported a correlation between HLA DQB1*0302 ($p_{corr} = .04$) and clearance of HCV infection compared with controls. This contrasts with the findings from our study group for the DQB1*0302 allele and clearance of HCV (Table 3). This apparent difference between the studies may reflect HLA frequency differences between the populations or skewing of results caused by comparisons between infected individuals and controls, as opposed to individuals who were exposed to HCV and either cleared the infecting virus or were persistently infected.

An interesting association with persistent HCV infection of DRB1*0701 in the absence of DQB1*0501 was identified in our study group. DRB1*0701 was recently reported to have association with inability to resolve HCV infection.[23] The DRB1*0701 allele has been associated with chronic hepatitis B virus infection, suggesting that the DRB1*0701 allele cannot present particular viral epitope(s) common to both hepatitis B and C viruses.

The HLA DRB1*11 allele group and the DQB1*0301 allele are reported by Minton et al.[25] as having an association with viral clearance. Neither of these associations were evident in our study group. Additionally, the DRB1*1104 and DQB1*0301 alleles have been found by many groups to occur with significantly greater frequency in those individuals who had a self-limiting HCV infection.[23,26,35,36] However, DRB1*1104 is reported to have an association with viral persistence in a recently reported investigation.[27] This apparent lack of agreement among studies may reflect both viral and study group heterogeneity and/or the influence of specific polymorphisms in immunoregulatory genes in linkage disequilibrium with the HLA class II alleles.[26,37] Evidence from the study presented here and others may lead to the

identification of crucial T-cell epitopes presented by HCV 1b–infected cells, which stimulate virus clearance.

In conclusion, individuals exposed to HCV 1b have immunogenetic factors that determine outcome after exposure to HCV 1b. Defined and homogeneous patient populations offer the best opportunity to illuminate previously disguised immunogenetic factors important in the clearance of HCV 1b.

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