IgM Antibody Response in Acute Hepatitis C Viral Infection

By John M. Clemens, Suhas Taskar, Kurt Chau, David Vallari, J. Wai-Kuo Shih, Harvey J. Alter, Joseph B. Schleicher, and Larry T. Mimms

IgM antibody against hepatitis C virus (IgM anti-HCV) was measured in serial samples from 15 transfusion recipients in whom posttransfusion chronic non-A, non-B hepatitis (NANBH) developed and three plasmasphere donors during acute HCV infection using recombinant proteins derived from three immunodominant regions: core, NS-3, and NS-4 (c100). IgM anti-HCV core was detected in 13 of 15 posttransfusion patients. Nine of these patients had transient, acute-phase IgM anti-HCV core detected coincidently or earlier than active IgG anti-HCV core response. The average duration of IgM anti-HCV core reactivity was 8.1 ± 3.7 weeks. One patient lacking an IgM anti-HCV core response had detectable IgM anti-HCV NS-3 during the acute phase. Passive transfer of IgM anti-HCV was not observed in these posttransfusion cases, in contrast to the high frequency observed for IgG anti-HCV. Late IgM anti-HCV was detectable against core, c100, and NS-3 in three, two, and one posttransfusion patients, respectively. These data indicate that IgM anti-HCV core is a useful acute-phase marker in HCV infection.

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0006-4971/92/7901-0030$3.00~0
based on a 50-member antibody-negative population; sample to cutoff ratio (S/CO) values greater than 1.0 were considered reactive. Effective removal of high titer IgG anti-HCV by the preincubation procedure was demonstrated by control incubation in which biotinylated goat anti-human IgG was substituted for the biotinylated goat anti-human IgM.

MATRIX HCV IgG test was conducted as described previously.3

RESULTS

Posttransfusion NANBH patients. Fifteen transfusion recipients in whom NANBH developed were assayed for the presence of IgM anti-HCV. In this study, serial bleeds were obtained from 10 patients over a short period (up to 66 weeks following surgery) and from five patients over a longer period (up to 10 years following surgery). The timing of posttransfusion IgG and IgM seroconversion is summarized in Table 1. IgG antibody reactivities to the recombinant HCV proteins for 14 of these patients were described previously by Vallari et al.4

Seroconversion to IgG anti-HCV was detected in all 15 patients by recombinant c100 and NS-3 antigens, and in 13 cases by core.4 Anti-HCV IgG was detected by core polypeptide as the earliest (n = 6) or simultaneously with the earliest marker (n = 4) in most cases. Detection of antibody by NS-3 as the earliest marker was observed in one case and was coincident with the earliest in five, and by c100 as the earliest or coincident with the earliest in two and three cases, respectively. Passive transfer of IgG antibody from donors was evident in 13 patients.1 Serological profiles of two of these patients are shown in Fig 1B and C. A serological profile of one of the two patients in which passive transfer was not observed is shown in Fig 1A. Also, in all five long-term patients (no. 11 to 15, Table 1), IgG was detected by all recombinant HCV proteins and persisted throughout the monitoring period, and up to 10 years in one patient.

Patterns and timing of IgM HCV reactivity differ significantly from the IgG response. Anti-HCV core was the only detectable IgM response in 12 patients and one patient showed only IgM anti-HCV NS-3 reactivity. In only two patients was an IgM response to multiple HCV epitopes evident. IgM anti-HCV responses were transient and occurred during acute illness in nine recipients who developed IgM anti-HCV core and in the single patient in whom IgM anti-HCV NS-3 was evident (Fig 1B). The first detection of IgM anti-HCV core coincided with IgG seroconversion in seven patients; IgM anti-HCV core was detected during the decline of passively transferred IgG anti-HCV in two patients. The mean interval to IgM anti-HCV seroconversion was 10.1 weeks after transfusion or 1.8 weeks from the onset of hepatitis (measured as the first elevation in serum ALT levels). The average duration of the IgM anti-HCV core response was 8.1 ± 3.7 weeks during the acute phase.

The acute phase IgM anti-HCV NS-3 response was coincident with first detection of IgG anti-HCV NS-3 and was 40 weeks in duration (Fig 1B).

Late onset of IgM anti-HCV core was evident in three of 15 patients. Two were transient and one (no. 13) had intermittent reactivity but remained positive at the time of the last bleed 364 weeks posttransfusion (Fig 1C). This patient was also reactive for IgM anti-HCV c100 at the last bleed date. Also, one patient (no. 12) showed late onset of IgM anti-HCV c100 and NS-3 at 37.6 weeks posttransfusion, but IgM titers had decreased to undetectable levels by 158 weeks posttransfusion.

Interestingly, no passive transfer of IgM anti-HCV was observed in these 15 patients. Overall titers of IgM anti-HCV core (usually S/CO < 10) were low, although patients no. 6 (Fig 1A) and 8 showed exceptionally high titers of IgM anti-HCV core during the acute phase.

Table 1. Weeks Posttransfusion of Anti-HCV IgG and IgM Seroconversion

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>ALT+</th>
<th>Matrix IgG*</th>
<th>Matrix IgM</th>
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<tr>
<td></td>
<td></td>
<td>c100</td>
<td>33Cl</td>
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<tr>
<td>1</td>
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<td>11.1</td>
<td>18.1</td>
<td>24.6</td>
</tr>
</tbody>
</table>

*Data from Vallari et al.4 Patients 8 through 15 correspond to patients 7 through 14, respectively, in ref 4.

†First date of active antibody response.

‡Interval of reactivity is indicated with hyphenated numbers, isolated number indicates only reactive draw in which IgM was detected.

§Indicates last available draw.

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Acute HCV plasmapheresis donors. Serial bleeds obtained from three plasmapheresis donors who developed acute HCV infection as measured by increased liver enzyme levels and seroconversion to anti-HCV were tested for the presence of specific IgM anti-HCV. All three donors developed IgM anti-HCV core, whereas negligible or no IgM anti-HCV reactivity was detected against NS-3 or c100. In two cases, IgM anti-HCV core was detected coincident with IgG anti-HCV core and, in one case, IgM anti-HCV core was detected in a draw before seroconversion to IgG anti-HCV core (Fig 2). IgM anti-HCV core was detectable coincident with an increase in ALT in two donors and 20 days after an ALT increase in one donor. Some decline in IgM core titers were observed with time, but all three donors were still reactive for IgM core at the last bleed obtained (50 to 85 days after the first ALT elevation).

DISCUSSION

Previous data have shown that addition of recombinant HCV core and NS-3 polypeptides to IgG anti-HCV assay containing c100 nearly eliminates the interval between the onset of hepatitis and the first detection of IgG antibody to HCV in posttransfusion NANBH patients. These studies also demonstrated that passive transfer of antibodies to HCV was primarily responsible for IgG anti-HCV positivity from 0 to 14 weeks after transfusion. Because of high level of passively transferred IgG anti-HCV in these patients, time of seroconversion and production of active IgG anti-HCV production resulting from HCV infection could only be assessed by measuring increasing levels of IgG anti-HCV. Since no passive transfer of IgM anti-HCV was detected in these patients, presence of IgM anti-HCV gave a clear indication of HCV infection and anti-HCV seroconversion (Table 1, Fig 1A to C).

The primary IgM anti-HCV response was against the core polypeptide in 13 of 15 posttransfusion NANBH cases and was also the only detectable IgM anti-HCV response in three plasmapheresis patients with acute HCV infection.
Only one posttransfusion patient had detectable IgM anti-HCV NS-3 during the acute phase and none had detectable IgM anti-HCV c100. IgM anti-HCV core was the first marker for active antibody response and seroconversion in three posttransfusion NANBH patients and in one acute-phase HCV plasmapheresis donor. However, appearance of IgM and IgG anti-HCV core usually occurred coincidentally. Data showed that IgM anti-HCV is not always limited to the acute phase of the disease, since some long-term chronic patients had protracted periods of IgM anti-HCV reactivity (Table 1). Similar results have been observed in chronically infected hepatitis B patients during reactivation of viral replication and exacerbation of liver disease.1,10

The duration of IgM anti-HCV core detectability was 8.1 weeks on average, but was considerably shorter in some patients. This window of IgM detectability may be missed in some acute-phase patients if specimens are not collected at short intervals.

These data indicate that IgM anti-HCV core is a useful marker for acute HCV infection in posttransfusion NANBH and in acute HCV infections in which the mode of transmission is unknown. However, the IgM response does not generally precede the IgG response, and thus detection of IgM is unlikely to narrow the window of seronegative infectivity that exists between the time of exposure and the first appearance of antibody.

Further study is required to determine the frequency of IgM anti-HCV in chronic HCV patients and whether IgM anti-HCV markers might be a useful measure of response to antiviral therapy in chronic patients.

ACKNOWLEDGMENT

We thank Sushil Devare, Jim Casey, and Suresh Desai for cloning and expressing recombinant HCV antigens. We also appreciate the work of Gerard Robey, Olivia Martin, Darwin Smith, and Rita Holzman for purification of these antigens. We thank Laurie Metz for typing the manuscript.

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