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 plasmapheresis 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 coincidentally 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.

The primary etiological agent of non-A, non-B hepatitis (NANBH), hepatitis C virus (HCV) has been sequenced and multiple immunodominant regions have been identified within the putative capsid (core), NS-3, and NS-4 (c100) regions.15 Recombinant proteins derived from these regions have been used in supplemental testing or confirmatory procedures.46

A study of 20 well-documented cases of posttransfusion NANBH reported that the mean delay to the development of anti-HCV was 21.9 weeks after transfusion and 15 weeks after onset of hepatitis if c100 alone was used in the immunoassay.2 Recently, Vallari et al. demonstrated that the use of a combination of recombinant HCV polypeptides enabled the detection of active antibody response in posttransfusion NANBH patients an average of 5 weeks earlier. The earliest marker in most cases was antibody against the HCV core protein. Passively transferred antibodies were detected in most posttransfusion NANBH patients and were a prominent feature of serology during the first 14 weeks posttransfusion.

Only antibody of IgG class is detected by current anti-HCV tests; however, IgM antibody class responses are the best markers of acute infection for both hepatitis A and B viral diseases. In this report, we describe the use of a semiautomated dot blot immunoassay to characterize IgM anti-HCV response in serial specimens from 15 posttransfusion NANBH patients and three HCV-infected plasmapheresis donors. These data demonstrate that IgM anti-HCV core may be useful in the diagnosis of acute HCV infection.
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.

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

<table>
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<th>Patient No.</th>
<th>ALT+</th>
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<tr>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>11.1</td>
<td>18.1</td>
<td>24.6</td>
</tr>
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</table>

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

1First date of active antibody response.

1Interval of reactivity is indicated with hyphenated numbers, isolated number indicates only reactive draw in which IgM was detected.

1Indicates last available draw.
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 gav 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.

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.

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