To the editor:

Maintenance of HCV-specific T-cell responses in antibody-deficient patients a decade after early therapy

Early therapy for hepatitis C virus (HCV) is associated with a high rate of viral clearance, but the long-term effects on immune responses remain controversial. The role of antibodies, both acutely and in the long term, is not clearly defined. We investigated these issues in a unique cohort of 7 individuals with primary antibody failure, who had received early interferon therapy after infection through contaminated immunoglobulin therapy a decade previously.

In 1994, an outbreak of hepatitis C virus infection, genotype 1a, occurred in 30 hypogammaglobulinemic patients in the United Kingdom from 1 batch of contaminated immunoglobulin. Treatment with interferon (IFN)–α was initiated within 6 months of inoculation, as reported previously.1,2 We were able to study 7 patients who had survived for 10 years, 5 remaining polymerase chain reaction–negative (PCR–) many years after treatment (or spontaneous resolution in 2 cases) and 2 who were still PCR+.

T-cell responses in peripheral blood were first studied using enzyme-linked immunospot assays with peptide pools spanning the whole HCV genome arranged in a matrix (described as matrix ELISpot), as well as specific human leukocyte antigen (HLA)–A2– and HLA-A1–restricted peptides.3 Incorporation of 3H-thymidine and CFSE (5,6-carboxylfluorescein diacetate succinimidyl ester; Molecular Probes, Eugene, OR) proliferation assays were performed, using recombinant HCV proteins NS3, NS4, and NS5 (Chiron, Emeryville, CA); HCV core peptide pools; tetanus toxoid (TT); or cytomegalovirus (CMV) lysis as previously described.4,5

Matrix ELISpot analysis revealed responses in 6 of 7 HCV-exposed patients (Figure 1A), but 0 of 5 hypogammaglobulinemic HCV-PCR– controls (P = .015). Strong HCV-specific responses were detected in all 5 HCV-exposed PCR– patients (Figure 1A-B) and 1 of 2 PCR+ patients.

CD8+ T-cell responses were examined using class I–restricted peptides in IFN-γ ELISpot. These were demonstrated in all patients tested (2 HLA-A2 and 1 HLA-A1; Figure 1A-B). We also analyzed HCV-specific CD4+ T-cell populations using a fluorescence-activated cell sorting (FACS)–based assay (Figure 1A,C), revealing substantial proliferation in 5 of 7 individuals. Responses to NS3-5, characteristic of immunocompetent spontaneous resolvers, were observed in 4 of 5 PCR– patients, but 0 of 2 PCR+ patients, and confirmed using conventional tritium assays.

Here we have shown a sustained response to antiviral therapy in acute HCV in the absence of specific antibody, associated with T-cell responsiveness maintained over a decade. Such activity was specific, was detected using a variety of methods, and included CD8+ and CD4+ T-cell responses. Two patients in the group did...
not receive therapy because they controlled the infection spontaneously, and these showed comparable responses in ELISpot and proliferation assays. Thus, the responses seen in these antibody-deficient patients who were IFN-α treated are not substantially different from untreated, spontaneously resolved, antibody-deficient individuals, or other spontaneous resolver cohorts, although a much larger cohort would be needed to assess this definitively.

The role of antibodies in long-term antiviral T-cell memory in humans is not known, although it plays a critical role in murine models. Single-source outbreaks of HCV have been highly informative as to the natural history of HCV infection and long-term outcomes of early treatment. Here, such an outbreak provides a unique insight into the longevity of T-cell responses in the absence of antibodies.

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This work was supported by grants from the Fritz Thyssen Foundation and the Wellcome Trust.

We thank all patients for their participation; Suranjith Seneviratne, Janet Burton, Nicola Salome-Bentley, and Carol Ross for assistance with samples and patients; and Rodney Phillips for continued support in The Peter Medawar Building.

References


To the editor:

Complete regression of cutaneous lesions of refractory Ph+ ALL after 4 weeks of treatment with BMS-354825

Imatinib (Glivec; Novartis, Basel, Switzerland), specifically inhibiting ABL kinase, has evidenced an important role in chronic myeloid and Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemias (ALLs); however, resistance is increasingly encountered, primarily mediated by mutations within the kinase domain of BCR-ABL that interfere with drug binding.

The second generation of tyrosine kinase inhibitors, which include BMS-354825 (Dasatinib; Bristol Myers Squibb, Princeton, NJ), also target ABL, but they appear able to bind also the majority of mutated forms of the protein.

We present the case of a patient with relapsed/refractory Ph+ ALL with disease at extramedullary (cutaneous) and blood level treated with BMS-354825 who achieved complete response in a very short period of time. This 67-year-old male patient was diagnosed with Ph+ ALL (70% Ph+ metaphases, p190 transcript) in September 2002. He was treated with...
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