OBJECTIVE: We will study the role of HCV in the pathogenesis of mixed cryoglobulinemia (MC), the putative protective role of monoclonal rheumatoid factors (mRF) in some patients with type II cryoglobulinemia (MC-2) and in addition evaluate the putative predictors of disease, the apo E E2 allele and the presence of clonal B cell populations.

RESEARCH PLAN and METHODS: In the glomerular and nerve lesions in patients with mixed cryoglobulinemia associated with HCV infection, the role of intact HCV will be determined by using an in situ hybridization assay for HCV RNA and antibody probes for structural and non-structural HCV antigens. Infection of mononuclear cells will be reassessed using an assay that will minimize false positive negative strand artifact, rTth polymerase mediated RT-PCR. Clonal B cell expansion (CBCE) will be detected by application of specific mRF sequences in MR extracted from peripheral B cells. The latter results will be correlated with ApoE phenotypes of patients determined in a commercial laboratory.

RESULTS: CBCE were examined in peripheral blood monocytes of 65 HCV-infected patients without MC, 8 HCV-infected patients with MC-2, 4 patients with MC-2 without HCV infection, 12 HCV-infected patients with type-3 MC (MC-3), and 33 normal individuals. DNA bands observed on analysis of CBCE were purified and sequenced. CBCE were detected in all patients with MC-2 (8 HCV-infected, 4 HCV negative) and in 10 HCV-infected patients without MC (15%), but were not observed in the MC-3 patients with or without HCV infection nor in the normal individuals. Immunoglobulin genes associated with the WA cross-idiotype (VH51pl, VK325, JH4, and JK1) and either of two characteristic D region sequences were present in 5 of HCV-infected MC-2 patients and in none of the MC-2 patients without HCV infection. The same genes were found in 3 of CBCE in HCV-infected patients not tested for MC (4.6%). Additional patients studied were HCV-infected patients with serum rheumatoid factors but without MC. Only two of twenty-four had a CBCE. The sequences were not known rheumatoid factors. Additional patients in this group are currently being recruited and a new control group. Patients with asymptomatic type II cryoglobulinemia are being recruited.

CLINICAL RELAVANCE: Detection of immunoglobulin gene characteristic of MC-2 associated with HCV infection in CBCE in HCV-infected patients may represent a potential marker for progression to MC-2.