BRIEF REPORT

Long-Term Outcomes of Patients With HCV-Associated Cryoglobulinemic Vasculitis After Virologic Cure

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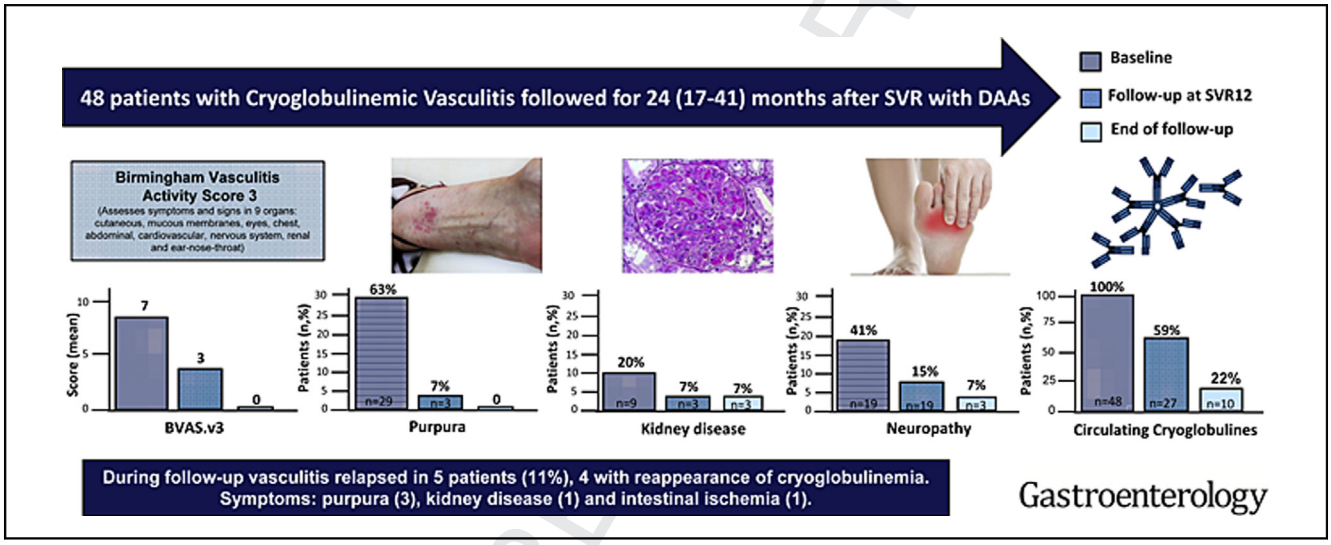

Patients with hepatitis C virus–associated cryoglobulinemic vasculitis (HCV-CV) have high rates of clinical remission after treatment with direct-acting antivirals (DAAs), but circulating cryoglobulins persist, and vascular disorders reappear in some patients shortly after DAA treatment ends. We performed a prospective study to assess the long-term clinical and immune system effects of HCV eradication with DAAs in 46 patients with HCV-CV and 42 asymptomatic patients with circulating cryoglobulins. A median of 24 months after DAA treatment (range, 17–41 months), 66% of patients with HCV-CV and 70% of asymptomatic patients with circulating cryoglobulins had an immunologic response, with comparable reductions in cryocrit from 2.6% to 0% ($P < .05$). However, 20% of patients still had positive test results for cryoglobulins after DAA therapy. Among patients with HCV-CV, 42 (91%) had a clinical response, in that their Birmingham Vasculitis Activity Score (version 3) decreased from 7 to 0 ($P < .01$). Nevertheless, within 2 years after a sustained viral response to DAA therapy, 5 patients with HCV-CV (11%, 4 with cirrhosis) had relapses of vasculitis that included severe organ damage and death.

Keywords: BVAS v3; Complication; Immunoglobulin; SVR.

Several studies of patients with hepatitis C virus (HCV)–associated cryoglobulinemic vasculitis (CV) have shown high rates of clinical remission 12–24 weeks after DAA therapy.[1–4] However, circulating cryoglobulins (CCs) may persist in up to 50% of patients after this short-term follow-up. Moreover, some reports have described relapse of vasculitic manifestations shortly after DAA cessation in the absence of B-cell disorders.[5,6] Thus, we prospectively assessed the long-term outcomes of a cohort

Abbreviations used in this paper: **ACC, asymptomatic circulating cryoglobulin; BVAS.v3, Birmingham Vasculitis Activity Score version 3; CC, circulating cryoglobulin; CH50, total hemolytic complement fraction; CV, cryoglobulinemic vasculitis; DAA, direct-acting antivirals; HCV, hepatitis C virus; RF, rheumatoid factor; SVR12, sustained virologic response 12 weeks after end of therapy.**

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of patients with HCV-related CV (HCV-CV) and asymptomatic CC (ACC) after HCV eradication with DAAs.

We evaluated 88 consecutive HCV-infected patients with CC. Among them, 46 (53%) met the criteria for HCV-CV,[7] and 42 (47%) had ACC. All patients achieved sustained virologic response 12 weeks after the end of therapy (SVR12). Most baseline features were similar between groups, including treatment regimen and duration (Supplementary Table 1). Among HCV-CV patients, the main clinical manifestations were purpura (63%), weakness (61%), neuropathy (41%), and nephropathy (20%).

Approximately 70% of patients had decreased C4 and total hemolytic complement fraction (CH50), and most HCV-CV patients had positive rheumatoid factor (RF). Cryocrit and RF levels were significantly higher in HCV-CV than ACC patients (2.8% vs 2.3%, $P = .04$ and 50 IU/mL vs 10 IU/mL, $P = .01$, respectively). Contrarily, C4 was significantly lower in HCV-CV patients than ACC patients (0.0 4 g/L vs 0.09 g/L, $P = .03$) (Supplementary Table 1).

The median duration of follow-up after DAAs was 24 (range, 17–41) months and was comparable in both groups. Among HCV-CV patients, 26 of 29 patients with purpura had resolved cutaneous lesions shortly after treatment finalization. Among patients with neuropathy (7 with sensory polyneuropathy, 6 with sensorimotor polyneuropathy, and 5 sensorimotor multiplex neuropathy), symptoms improved in 12 of 19 patients at SVR12 and in 4 additional patients throughout follow-up. The median Neuropathy Total Symptom Score–6 score decreased from 2.3 (range, 1.16–4.80) at baseline to 1 (range, 0–3.66), ($P < .05$); complete neurologic response increased from 10% at SVR12 to 47% at last follow-up. Among patients with nephropathy, 6 of 9 experienced a complete recovery at SVR 12, but the remaining 3 did not improve further (Table 1). Also, in 1 patient with intestinal involvement and 3 with Sicca syndrome, these manifestations resolved at SVR12 and remained asymptomatic overtime.

As a result, comparing SVR12 with the last follow-up evaluation, complete clinical response increased from 70% to 80% and partial response from 9% to 11%. Thus, only 4 (9%) patients were nonresponders at the last evaluation. Duration of HCV infection and CV manifestations did not affect overall clinical response. Assessment of clinical improvement by BVAS.v3 showed that the score decreased from a median of 7 (range, 2–31) at baseline to 3 (range, 0–11) at SVR12 ($P < .05$) and to 0 (range, 0–8) at last follow-up ($P < .05$) (Table 1). Interestingly, a BVAS.v3 ≤ 9 at entry was associated with complete clinical response (hazard ratio, 3.3 [range, 1.4–8.0]; $P = .01$).

At the immunologic level, cryoglobulins persisted in 59% and 45% at SVR12 in HCV-CV and ACC patients, respectively, and in only approximately 20% of both groups at last follow-up (Table 1). Patients with persistent CC had a higher baseline cryocrit (Supplementary Table 2). Complement and RF values also improved in both groups but remained abnormal in up to 22% and 14% among patients in the HCV-CV and ACC groups, respectively (Table 1). Overall, complete immunologic response increased from 43% at SVR12 to 68% at last follow-up (from 39% to 66% in HCV-CV patients and from 50% to 70% in ACC patients, $P < .05$). Neither DAA therapy duration (12 vs 24 weeks) nor different treatment regimens had an impact on clinical and immunologic outcomes.

Regarding immunosuppressive therapy, glucocorticoids were either reduced or withdrawn at last follow-up (Table 1). Three patients had received rituximab, but the last cycle was administered more than 36 months before DAAs. Overall clinical and immunologic responses were similar between patients who received immunosuppressive therapy and those who did not (Supplementary Table 3).

Although most vasculitic manifestations resolved or improved, 5 patients presented with a vasculitis relapse during follow-up, 4 with underlying cirrhosis. Three patients had transient episodes of purpura a median of 6 months after the end of treatment. One patient developed nephrotic syndrome and another died of acute mesenteric ischemia 1 year after SVR12. Interestingly, cryoglobulin test results became positive or increased in 4 of the 5 of patients with relapse (Table 2). Characteristics of patients with or without vasculitis relapse are detailed in Supplementary Table 4. No patient with ACC developed an overt CV during the study.

Because most published studies assessing the impact of HCV eradication on CV are based on short-term follow-up,[1–4] we believe that our prospective long-term follow-up analysis will help clinicians. An extended follow-up (up to 2 years) of our HCV-CV cohort correlates with a significant improvement in clinical response, reaching 90% of patients. This was confirmed by a significant decrease in BVAS.v3 score and the withdrawal of immunosuppressive therapy in >90% of patients. This is extremely reassuring for those individuals who, despite HCV cure, are still symptomatic at