HCV and Autoimmunity: New Details Emerge

Ongoing research focuses on the role of B-lymphocyte stimulator protein in promoting B-cell proliferation.

BY NANCY WALSH
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The link between chronic hepatitis C infection and the onset of disordered autoimmunity continues to grow in both certainty and complexity, with new pathogenic insights emerging and with important implications for diagnosis, treatment, and prognosis.

Since identification of the hepatitis C virus (HCV) in 1989, it has become clear that the chronic infection can be accompanied by a variety of systemic autoreactive phenomena, most notably vasculitis.

This virus replicates very rapidly, turning over billions of times each day and chronically stimulating the immune system, said Dr. Leonard H. Calabrese, professor of medicine at Case Western Reserve University, Cleveland.

In approximately half of patients, this chronic immune stimulation leads to the development of autoreactivity and the appearance of rheumatoid factor (RF) in serum. Some patients also are found to have cryoglobulins, and a subset develop autoimmune conditions such as cryoglobulinemic vasculitis with symptoms of purpura, glomerulonephritis, peripheral neuropathy, and polyarthritis. B-cell lymphomas also can occur.

These patients represent a diagnostic challenge. Clinical suspicion for the virus must remain high because most patients infected with HCV remain undiagnosed and because they can present not only with hepatic abnormalities but with a wide range of vasculitis-associated symptoms, he said.

Treatment is problematic too. "The first issue is whether or not [patients] need treatment for the hepatitis, and it's necessary to bring in the resources of hepatology to make this determination," Dr. Calabrese said in an interview.

In many patients, aggressive antiviral treatment with peginterferon and ribavirin will clear both the virus and the autoimmune symptoms. However, in some patients, symptoms of vasculitis persist despite treatment, and in at least half of patients the viral infection is not controlled or the treatment cannot be tolerated. These patients pose significant therapeutic challenges, according to Dr. Calabrese, because standard treatments for vasculitis are immunosuppressive, and these patients have a lifelong, potentially lethal infection that could worsen with the use of agents such as glucocorticoids.

Other therapeutic strategies being investigated include the use of rituximab to target the B cells that are the source of the autoantibodies, but the data with this agent are preliminary and the numbers are small, he said.

In some but not all cases, aggressive treatment of hepatitis C virus infection with peginterferon and ribavirin will clear the autoimmune symptoms.

Another new approach involves targeting a factor known as B-lymphocyte stimulator (BLyS), which has been linked in recent reports with both HCV and autoimmunity.

BLyS is a protein belonging to the tumor necrosis factor superfamily that was first discovered by scientists at Human Genome Sciences, Rockville, Md., in 1999. It is secreted by monocytes, macrophages, and dendritic cells and promotes differentiation and proliferation of autoreactive B cells, and its overproduction can disrupt immune tolerance by inhibiting B-cell apoptosis. It is known to be upregulated in some patients with systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren's syndrome.

One group of researchers from L'Hôpital Pitié-Salpêtrière, Paris, recently reported on 76 consecutive HCV-infected patients, 47 (62%) of whom were positive for mixed (types II and III) cryoglobulins, and 27 (36%) of whom had systemic vasculitis. Arthralgias were present in 30 (40%), purpura in 20 (26%), peripheral neuropathy in 19 (25%), and glomerulonephritis in 6 (8%).

Significant correlations were seen in BLyS levels, cryoglobulin levels, RF positivity, arthralgias, and the presence of systemic vasculitis among these HCV-positive patients. On multiple regression analysis, the presence of type II cryoglobulins was associated with high levels of BLyS, with a correlation coefficient of 0.406 (Rheumatology 2007;46:65-9).

One of the investigators, Dr. Patrice Cacoub, confirmed in an interview that his findings support the linkage of BLyS overexpression with HCV-induced autoimmunity. Of his findings he wrote, "They also create an exciting prospect for the use of anti-BLyS antibodies or decoy BLyS receptors in the future therapeutic algorithm of HCV-infected patients with severe mixed cryoglobulins-associated vasculitis." He and his colleagues also noted that the mechanisms involved in B-cell proliferation associated with HCV infection are incompletely understood and suggested that induction of the anti-apoptotic gene Bc12 may be involved.

A second group of researchers from Israel studied 65 patients with chronic HCV infection, comparing them with 57 patients with SLE and with 15 patients with chronic hepatitis B virus (HBV) infection, with 35 healthy volunteers acting as controls.

Mean serum BLyS level in patients with HCV was elevated, at 2.4 ng/mL. The mean level among patients with SLE was 3.1 ng/mL, while it was only 1.1 ng/mL in both HBV patients and healthy controls.

Serum levels of BLyS were elevated in 29% of patients with HCV and in 32% of patients with SLE but in none of the healthy patients.

Among the HCV-infected patients, elevated BLyS levels also were associated with the presence of arthralgias, anticardiolipin antibodies, and cryoglobulins. A total of 89% of those with elevated BLyS had detectable cryoglobulins, compared with 23% of those with normal levels of BLyS (J. Autoimmunity 2006;27:134-9).

Another group of researchers from northern Italy reported on 66 patients with mixed cryoglobulinemia and frank vasculitis, 54 (82%) of whom were positive for HCV. They compared this group with 33 HCV-positive patients who were either cryoglobulin negative or had detectable cryoglobulins but were asymptomatic, and with 48 healthy blood donors. They found a significantly higher frequency of BLyS positivity, both among patients with mixed cryoglobulinemia and among those who were HCV positive without evidence of cryoglobulins.

These investigators also noted that their finding of a subgroup of patients with mixed cryoglobulinemia without HCV infection suggests that other infectious agents also may be capable of triggering the BLyS deregulation that results in the formation of cryoglobulins (Rheumatology 2007;46:37-43).

The need for investigations into other possible etiologic factors also was highlighted in a recent presentation at the International Congress on Autoimmunity in Sorrento, Italy. Dr. Jan Willem Cohen Tervaert reviewed the experience at the University Hospital Maastricht, the Netherlands, where 22 patients with cryoglobulinemia have been treated during the past 5 years—none of whom had HCV detectable either serologically or by polymerase chain reaction. In the Netherlands, the prevalence is low, at 0.098%, with infection found primarily among drug users and immigrants, he said.

In this group of patients, 86% had constitutional symptoms such as fever and malaise. Skin vasculitis and glomerulonephritis each were present in 41%, arthritis in 73%, and peripheral neuropathy in one-third. C-reactive protein was elevated in 73%, RF was present in 67%, and complement levels were low in 70%. Despite the fact that none of the patients had HCV infection, liver function abnormalities were seen in 36%, Dr. Cohen Tervaert said. Two had vasculitis associated with lymphoproliferative disease and 10 also had connective tissue diseases such as Sjögren's syndrome and SLE.

This series demonstrated that non-HCV cryoglobulinemia tends to be more severe than when the autoimmune disorder results from HCV, he said.

This observation also was made by Dr. Cacoub's group in Paris, who compared 65 patients with non-HCV cryoglobulinemia with 118 patients with HCV infection and cryoglobulinemia. The non-HCV patients had a fourfold increased risk of developing B-cell non-Hodgkins lymphoma (Arch. Intern. Med. 2006;166:2101-8). ■

Many Atherosclerotic Risk Factors May Go Untreated in Lupus

BY JEFF EVANS
Senior Writer

WASHINGTON — Awareness of the increased risk of premature atherosclerosis in lupus patients may be rising, but even experts in lupus treatment are inadequately treating patients with known risk factors for the condition, Dr. Murray B. Urowitz reported at the annual meeting of the American College of Rheumatology.

Dr. Urowitz, director of the Centre of Prognosis Studies in the Rheumatic Diseases at Toronto Western Hospital and his colleagues in the Systemic Lupus International Collaborating Clinics (SLICC), a group of 30 investigators located at 27 centers around the world, conducted an analysis of 935 SLE patients who had been enrolled in the multicenter registry within 15 months of diagnosis during 2000-2006. Follow-up data at 3 years were available for 278 patients. These patients had a mean SLE disease activity index-2k (SLEDAI-2k) score of 5.49 at enrollment and an adjusted mean SLEDAI-2k over 3 years of 4.94.

Of 101 patients who had hypercholesterolemia at enrollment, 25 received treatment for the condition. After 3 years, 167 patients had ever had hypercholesterolemia, but only 63 (38%) had received treatment.

In comparison, the percentage of hypertensive patients who received treatment increased from enrollment (87 of 109 [80%]) to the 3-year follow-up (144 of 162 [89%]) even though the prevalence of hypertension increased.

Other risk factors for coronary artery disease increased in prevalence during the 3 years, including the percentage of patients who currently or ever had smoked (from 14% to 19% and from 37% to 42%, respectively), the percentage of patients who reported a family history of coronary artery disease (from 18% to 25%), as well as the percentage of those with diabetes mellitus or those who had become postmenopausal.

Risk factors relating to body composition also increased during follow-up, such as the percentage of patients with a body mass index in the overweight or obese range (from 31% to 46%), a waist:hip ratio greater than 0.8 (from 32% to 55%), and low physical activity (from 37% to 55%). Since enrollment, more patients had taken corticosteroids (from 71% to 79%), antimalarials (from 60% to 77%), or immunosuppressives (from 38% to 59%).

"All risk factors increased in prevalence over 3 years, so you're not off the hook when they start [treatment]," he said. ■