Hepatotropic Viral Infection Associated Systemic Vasculitides—Hepatitis B Virus Associated Polyarteritis Nodosa and Hepatitis C Virus Associated Cryoglobulinemic Vasculitis

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Two hepatotropic viruses have been shown to have causal relationship with systemic vasculitis-hepatitis B with classical polyarteritis nodosa and hepatitis C with cryoglobulinemic vasculitis. The present paper provides an updated overview on the clinical presentations and management of these vasculitides.

HBV associated PAN patients have higher weight loss, peripheral neuropathy, mononeuritis multiplex, abdominal pain, gastrointestinal manifestations requiring surgery, cardiomyopathy, orchitis, hypertension, and/or elevated transaminase levels. Microaneurysms are also more common in mesenteric artery. Skin manifestations, however are less common. These patients also have a severe disease as suggested by higher five factor score and higher BVAS. Though relapses are less common, mortality is higher in patients with HBV PAN as compared to non HBV PAN. Plasmapheresis has a role in treatment in clearing off immune complexes.

The common clinical manifestations of HCV associated cryoglobulinemic vasculitis are skin lesions, peripheral neuropathy, glomerulonephritis, arthritis, and sicca symptoms. Though combination therapy comprising of pegylated interferon α and ribavirin is the first line of management, immunotherapy is needed for severe or life threatening manifestations. Recent randomized trials have shown the efficacy of rituximab in such situations. (J CLIN EXP HEPATOL 2013;3:204–212)

There is a complex relationship between vasculitis and infection.¹ Though various infectious agents have been attributed as the underlying cause of several vasculitides, a true causal association has been established only in a few situations. Two hepatotropic viruses have been demonstrated to be the cause of systemic necrotizing vasculitis; Hepatitis B (HBV) for classical polyarteritis nodosa (PAN) and hepatitis C virus (HCV) for cryoglobulinemic vasculitis.²

POLYARTERITIS NODOSA (PAN)

PAN is a medium vessel vasculitis associated with HBV infection. Though PAN was first described by Kussmaul

and Maier in 1861, but the first description of its association with HBV was given by Tre'po et al and Gocke et al in 1970.^{3–5} HCV positivity has occasionally been observed in patients with PAN, but it is not considered to be a major etiological factor; and is often observed concomitantly with other viral infections like HBV.^{6–8}

Incidence

The reported annual incidence of PAN in general population varies widely from a low of 4.6 per 1,000,000 to as high as 77 per 1,000,000 in hepatitis B hyperendemic Alaskan population.^{9,10} Over the years, the frequency of HBV infection, and thus associated PAN, has come down due to screening of blood products before transfusion and increasing vaccination.^{11,12} The frequency of HBV associated PAN amongst all patients of the French vasculitis group (FVG) has come down from a high of 48.8% in five years (1982–1986) to 17.4% in six years (1997–2002).^{11,13}

Mechanism of Vasculitis

The exact pathogenesis of PAN largely remains unknown and has not been extensively investigated.¹¹ It is supposed to be a type III or immune complex reaction where the immune complexes precipitate and get trapped in the vessel walls resulting in vascular injury (Figure 1).^{14–18}

Keywords: HBV, polyarteritis nodosa, HCV, cryoglobulinemic vasculitis

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Abbreviations: PAN: polyarteritis nodosa; FVG: French vasculitis group; FFS: five factor score; BVAS: Birmingham vasculitis activity score; CHCC: Chapel Hill Consensus classification criteria; MPA: microscopic polyangiitis; ANCA: anti neutrophilic cytoplasmic antibodies; HBV: hepatitis b virus; HCV: hepatitis c virus; MPO: myeloperoxidase; PE: plasma exchange

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Figure 1 Schematic representation of pathogenesis of HBsAg associated polyarteritis nodosa.

HBsAntigen and anti-HBs antibody immune complexes have been demonstrated in the vascular lesions in these patients. The presence of large masses of HBsAg immune complexes in the recent vascular lesions, lesser amount of these complexes in healing lesions and their absence in healed lesions points toward the primary role played by the immune complexes in the pathogenesis of these vascular lesions.¹⁹ This has also been the basis of therapeutic strategies to clear immune complexes. There is no clear answer as to the question as to why only a small number of patients with hepatitis B infection develop PAN?

CLINICAL FEATURES

The clinical manifestations of HBV associated PAN are largely similar to non HBV associated PAN. The common clinical manifestations are listed in Table 1. General symptoms of PAN include fever, malaise and weight loss. The fever characteristics may vary from high grade to remittent or intermittent. Intense diffuse myalgias are also frequent. Neurological manifestations are commonly confined to peripheral nerves and CNS involvement is rare. But whenever, CNS involvement is present, it denotes poor prognosis.²⁰ Skin manifestations are livedo reticularis, livedo racemosa, skin nodules and cutaneous infarcts. The arterial occlusions can result in digital gangrene. Lungs are usually spared in PAN, though a case of HBV associated PAN patient with multiple lung nodules has been reported in which nongranulomatous necrotizing vasculitis involving small pulmonary arteries was confirmed.²¹ Variable degree of renal insufficiency may occur due to vascular nephropathy and renal infarction. Presence of glomerulonephritis goes against the diagnosis of classical PAN. Cardiac and

gastrointestinal involvement are the other major manifestations of PAN.

In patients with HBV associated PAN, an increased frequency of orchitis, vascular nephropathy and malignant hypertension was reported from an initial report of 41 patients from the French vasculitis group (FVG).¹³ In a subsequent study of 348 patients of PAN from the same group [non HBV associated PAN ($n = 225$), HBV associated PAN ($n = 123$)], patients with HBV associated PAN had more severe disease as suggested by higher five factor score (FFS) and higher Birmingham vasculitis activity score (BVAS).²² HBV associated PAN patients had higher weight loss, peripheral neuropathy, mononeuritis multiplex, abdominal pain, gastrointestinal manifestations requiring

Table 1 Clinical manifestations of HBV associated PAN and HCV associated cryoglobulinemic vasculitis.

HBV associated PAN

Fever, malaise and weight loss
Arthralgias
Hypertension
Peripheral neuropathy
Skin manifestations like palpable purpura, livedo reticularis and skin ulcers
Peripheral vascular manifestations like gangrene
Orchitis
Abdominal pain, gastrointestinal bleeding
Tachycardia, congestive cardiac failure

HCV associated cryoglobulinemic vasculitis

Skin manifestations like palpable purpura, painful skin ulcers
Arthralgias/arthritis
Peripheral neuropathy
Renal involvement in form of hypertension, microscopic hematuria, proteinuria

surgery, cardiomyopathy, orchitis, hypertension, and/or elevated transaminase levels.²² Microaneurysms were also more common in mesenteric artery and not in renal artery in HBV associated PAN. Skin manifestations, however, were less common in HBV associated PAN.²² Hepatitis and jaundice at PAN onset has been reported very infrequently.¹¹ Microaneurysms in renal vessels are shown in Figure 2. In patients with PAN, the routes of hepatitis b transmission have been identified to be heterosexual, intravenous drug abuse, blood transfusions and surgical procedures. The risk of transmission due to blood transfusions was there when there were no screening strategies for blood products.

Timing of Polyarteritis Nodosa with Relation to Hepatitis B Virus Infection and Manifestations of Hepatitis B Virus Infection

PAN usually occurs early in the course of HBV infection. When it was possible to time the acquisition of HBV infection, that is, date of blood transfusion or sexual transmission, the mean interval between HBV infection and first manifestation of PAN was 596 ± 628 days (range 30–1695 days). The mean time between diagnosis of hepatitis and PAN was 217 ± 800.9 days. One patient developed fatal fulminant hepatic failure at the time of seroconversion.¹¹

Hepatic Involvement in Patients with Hepatitis B Virus–Polyarteritis Nodosa

Hepatitis is common and usually mild. Clinical manifestations in patients diagnosed to have hepatitis before PAN were of asthenia and mild increase in transaminases, and jaundice was usually absent. Simultaneous occurrence of

hepatitis and PAN was also observed in some patients, supporting the fact that PAN is exacerbation of systemic manifestations seen in early phase of hepatitis.¹¹ The prodromal phase of hepatitis is exacerbated in PAN, and there is only moderate rise in transaminases as compared to usual response in which there is jaundice and steep rise in transaminases. Deposition of immune complexes is associated with the systemic manifestations observed in HBV PAN.

DIAGNOSIS

The diagnosis of PAN for research purposes has been based upon ACR and more importantly Chapel Hill consensus classification criteria (CHCC).^{23,24} ACR 1990 criteria do not distinguish PAN and microscopic polyangiitis (MPA), the latter being formally defined by CHCC nomenclature of systemic vasculitides in 1994.²⁴ A revised international CHCC nomenclature of vasculitides has been published recently.²⁵ In this revised nomenclature, HBV associated PAN and HCV associated cryoglobulinemic vasculitides have been kept in a separate group labeled as vasculitis associated with probable etiology. The other vasculitides in this group are syphilis associated aortitis, drug associated immune complex vasculitis, drug associated ANCA associated vasculitis and cancer associated vasculitis.

Though HbsAg positivity is one of the ten criteria of ACR classification system, with presence of three of these ten criteria required to make a diagnosis of PAN, recent attempts to make a PAN diagnostic criteria from FVSG database of 949 patients replaced HBsAg with markers reflecting active HBV replication.^{26,27} This criteria included three positive discriminant criteria like markers reflecting active HBV replication such as the presence of HBeAg in serum and/or the detection of HBV DNA at 10^5 copies/ml; arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes; and development of mononeuropathy, multiple mononeuropathies, or polyneuropathy. This also included five negative discriminant criteria—presence of ANCA in serum, as determined by indirect immunofluorescence; personal antecedents of asthma; signs of maxillary sinusitis or otitis media; detection of cryoglobulins in serum; and signs of glomerulopathy, such as proteinuria and/or hematuria, with or without renal insufficiency, not due to urinary tract infection, urolithiasis, or hematologic or other nonglomerular causes.²⁶ A reliable classification system of vasculitis has recently been devised which can help in differentiation of PAN from small vessel vasculitis.²⁸ The presence of Anti neutrophilic cytoplasmic antibodies (ANCA), glomerulonephritis and/or histological involvement of arterioles, capillaries, and/or venules goes in favor

Figure 2 MIP images showing microaneurysms in kidney.

of small vessel vasculitis and against the diagnosis of PAN. Both indirect immunofluorescence (IIF) and ELISA methods should be employed for doing the ANCA.²⁹ There may be occasional ANCA positivity on IIF of perinuclear (p ANCA) or atypical ANCA pattern but ELISA positivity against myeloperoxidase (MPO) and proteinase-3 (PR3) does not occur. The abdominal and renal angiographic findings included microaneurysms (Figure 2), vessel stenosis or visceral infarcts like renal infarcts.

PREDICTORS OF RELAPSE AND MORTALITY

Relapses are less common in HBV associated PAN as compared to non HBV associated PAN.²² In a multivariate analysis, the other predictors of relapse besides the non HBV status (HR 2.27 [95% CI 1.11–4.630]) were skin manifestations (HR 1.85 [95% CI 1.08–3.23]) more so when only skin nodules were considered (HR 2.21 [95% CI 1.30–3.78]). The patients diagnosed to have PAN after 1995 had better outcome. Though the patients with HBV associated PAN had higher mortality as compared to non HBV associated PAN, but the multivariate analysis did not show HBV positive status as independent predictor of mortality.²² This might mean that these patients had more aggressive disease. The cause of death could be related to basic disease, treatment side effects or unrelated.⁶ In all forms of systemic necrotizing vasculitis, early multisystem involvement, especially gastrointestinal is often fatal.³⁰ Five factor score (FFS) given by the French vasculitis group can be used to evaluate prognosis in patients with PAN, Eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg–Strauss syndrome) and Microscopic polyangiitis.³¹ While calculating FFS, a score of one is given for each of the following factors; proteinuria >1 g/24 h, Creatinine >140 μ mol/l, specific gastrointestinal involvement, specific cardiomyopathy and specific central nervous system involvement. Five years survival rate and relative risk of death with FFS of 0 was

88.1% and 0.62; FFS of 1 was 74.1% and 1.35; and FFS of ≥ 2 was 54.1% and 2.40 respectively.⁶ BVAS (Birmingham vasculitis activity score) is the most widely used tool to quantify disease activity in systemic small vessel vasculitis. The present version (version 3) consists of 56 items with a maximum score of 63.³²

Treatment with corticosteroids and cyclophosphamide help virus persistence and facilitate development of chronic hepatitis and cirrhosis thus cyclophosphamide and prolonged corticosteroids are contraindicated.⁶ Both immunosuppression and plasmapheresis due to its central venous access predispose these patients to infections and thus associated mortality. HBV PAN is associated with higher mortality as compared to non HBV associated PAN.²²

TREATMENT

Though many landmark randomized trials have been possible in systemic vasculitides due to international collaborative efforts, but it has not been possible to do a randomized trial in HBV PAN due to its rarity.¹¹ Therapeutic strategy is based upon the understanding of pathogenesis of HBV PAN, thus targeting clearance of immune complexes with plasma exchange (PE) and suppression of HBV replication with antiviral drugs (Table 2). Corticosteroids are instituted for the initial two weeks in an attempt to control the ongoing organ or life threatening inflammatory process. Abrupt stoppage of corticosteroids results in enhanced immunological clearance of HBV infected hepatocytes and favors seroconversion from HBsAg to anti HBe antibody. Subsequently, PE and anti-virals become the cornerstone of therapy.¹¹ Deposition of immune complexes is the major determinant of vessel inflammation and these are removed by PE. Anti-virals also facilitate the immune complex clearance by decreasing the viral load.¹¹

When HBV associated PAN was treated like non HBV associated PAN with steroids and cytotoxic drugs, with

Table 2 Treatment of HBV associated PAN and HCV associated cryoglobulinemic vasculitis.

HBV associated PAN		
Short course of steroids (two weeks) with appropriate antiviral agent and plasmapheresis		
HC associated cryoglobulinemic vasculitis		
Mild to moderate disease manifestations	Purpura, arthralgias, arthritis, peripheral neuropathy	Antiviral agents only (Peg IFN α + ribavirin, Peg IFN α + ribavirin + protease inhibitor for HCV genotype 1)
Severe disease manifestations	Worsening renal functions Mononeuritis multiplex Extensive skin disease including distal necrosis	Immunosuppression + antiviral agents (e.g. rituximab + Peg IFN α + ribavirin)
Life threatening manifestations	RPRF, GI, cardiac, pulmonary and CNS involvement Peripheral necrosis of extremities Signs of hyperviscosity	Plasmapheresis + immunosuppression initially Followed by antiviral therapy

Peg IFN α = pegylated interferon alpha, RPRF = rapidly progressive renal failure, GI = gastrointestinal, CNS = central nervous system.

treatment was effective initially but there were increased relapses and complications due to virus persistence resulting in chronic hepatitis and liver cirrhosis.¹⁰ PE in combination with antiviral was shown to be effective in management of HBV PAN in 1988.^{33,34} As vidarabine was the first antiviral agent available, a combination of three-week course of vidarabine with PE after a week of corticosteroids resulted in complete clinical recovery in three quarter of patients.³⁵ Though HbeAg to anti HBe antibody seroconversion was observed in half of the patients, HBsAg to anti HBsAg antibody seroconversion occurred only in 18%. Limited efficacy of vidarabine and early integration of virus genome into hepatocytes was attributed to be the cause of this low seroconversion. Subsequently it is shown that other antiviral agents like interferon α (IFN α) and lamivudine gave better results than vidarabine.^{36,37} The dose of IFN α is the same as that for hepatitis B (3 million units), thrice a week initially and if seroconversion does not occur at 4–6 months then the dose should be increased to 6 million units thrice a week. Majority of patients tolerate the therapy well and do not require it for more than 6 months. Lamivudine 100 mg/day along with PE after a few days of corticosteroids therapy was associated with recovery in 90% patients and seroconversion to HBe antibody status in 60% patients.³⁷ PE can clear the immune complexes responsible for the disease. Though PE may control the disease without addition of steroids, steroids are commonly prescribed in beginning for a few days for rapid control of clinical manifestations. The schedule of PE is: 4 sessions/week for 3 weeks, then 3 sessions/week for 2–3 weeks. The interval between the sessions is increased subsequently. Appearance of antibodies against the virus should be the endpoint of PE. Quantitative measurement of viral DNA would be required in a few cases with fluctuating antibody levels. The newer antiviral agents like adefovir dipivoxil, entecavir, telbivudine and tenofovir are potentially useful for treatment of HBV PAN but the trial evidence is lacking due to difficulty in setting up the trials due to decreasing numbers of HBV PAN patients over the last few decades (6).

HEPATITIS C VIRUS ASSOCIATED CRYOGLOBULINEMIC VASCULITIS

The association between HCV and cryoglobulinemia has been established since many years and it is predominantly type 11 cryoglobulinemia. Though mixed cryoglobulinemia was described more than four decades ago, its association with HCV became evident after the discovery of HCV in 1989 and the subsequent demonstration of serological evidence of HCV in significant number of patients with mixed cryoglobulinemia and chronic liver disease.^{38–40}

PATHOGENESIS

The epidemiological, pathological and basic research studies have definitely established the role of HCV infection in cryoglobulinemic vasculitis. Detection of HCV RNA in the different target tissues by the *in situ* hybridization confirm the direct involvement of HCV in the immune complex mediated vascular lesions and the underlying lymphoproliferative disorders.⁴¹

As only a fraction of those people with HCV and detectable cryoglobulinemia go on to be able to develop cryoglobulinemic vasculitis, HCV itself may not be able to propagate the pathogenetic processes. Chronic stimulus due to HCV may facilitate clonal B cell expansion.^{42,43}

CLINICAL FEATURES

HCV infected patients can have cryoglobulinemia but it remains asymptomatic in most of them. Cryoglobulinemic syndrome is a condition resembling serum sickness for which a criteria has been proposed (1) cryocrit >1% for at least 6 months, (2) rheumatoid factor positivity or C4 >8 mg%, and (3) at least two of the following: purpura, weakness, arthralgias.⁴⁴

The common clinical features of cryoglobulinemic vasculitis are skin lesions in the form of skin lesions, peripheral neuropathy, glomerulonephritis, arthritis, and sicca symptoms.⁴⁵ The common clinical manifestations are listed in Table 1.

Skin Manifestations

Purpura is the most common manifestation. The lesions are palpable, polymorphic and usually confined to the legs, though trunk may also be involved occasionally. These manifestations are aggravated by prolonged standing and cold weather. Long standing purpuric lesions leave ocherous pigmentation. Painful skin ulcers over the lower limbs, mostly over malleoli, denote aggressive disease requiring aggressive management. Raynaud's phenomenon is also seen in some patients and may be the first manifestation.

Arthralgias/Arthritis

Mild, intermittent, non-erosive joint involvement is seen in about 10% of patients. Some patients may have myalgias or polymyalgia rheumatic like presentation.

Nervous System Involvement

The frequency of nervous system involvement is reported to be 17–62% and at times it may be the first manifestation.^{46,47} Deposition of immune complexes in epineural vessels leading to vasculitis cause the ischemic damage to the nerves which is reflected as axonal damage on electrophysiological studies.⁴⁸ The symptoms are paresthesias, painful dysaesthesias, and myalgias. The course of

neuropathy is chronic and may at times be relapsing.⁴⁹ Mononeuritis multiplex, though reported, is rare. Central nervous system involvement in form of transient dysarthria, hemiplegia and acute confusional state is also rare.⁵⁰

Renal Involvement

Renal involvement can be present in 20% patients at the time of diagnosis and is seen in upto 30% patients with MC during the course of illness.⁵¹ Cryoglobulinemic nephropathy is a distinct pathological entity.⁵² Though the mechanism of HCV induced renal damage is not clearly defined, deposition of immune complexes has been suggested to play a major role in the pathogenesis.⁵³ The clinical manifestations are hypertension, microscopic hematuria, red blood cell casts, proteinuria. The course is indolent in most of the patients. Nephrotic syndrome (21%) and nephritic syndrome (14%) are less common.⁵⁴ Upto 14% patients with develop chronic renal failure after a mean follow up of six years.⁵⁵

Pulmonary and gastrointestinal involvement are less common.^{56,57}

PRELIMINARY CLASSIFICATION CRITERIA FOR THE CRYOGLOBULINAEMIC VASCULITIS

A preliminary classification criteria has been published for cryoglobulinaemic vasculitis recently. Presence of serum cryoglobulins in at least two determinations at ≥ 12 weeks interval is an obligatory requirement for fulfillment of these classification criteria. There are three items (questionnaire, clinical and laboratory), and presence of two of these three items is required for making a diagnosis. The questionnaire item requires presence of two of the following three to be counted: Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?; Have you ever had red spots on your lower extremities which leave a brownish color after their disappearance?; Has a doctor ever told you that you had viral hepatitis?

The second item is the clinical item, which requires at least three of the following four (present or past) to be counted.

• Constitutional symptoms	Fatigue, Low grade fever (37–37.9 °C, >10 days, no cause), fever (>38 °C, no cause), fibromyalgia
• Articular involvement	Arthralgias/arthritis
• Vascular involvement	Purpura/skin ulcers/necrotising vasculitis/hyper viscosity syndrome/Raynaud's phenomenon
• Neurological involvement	Peripheral neuropathy, cranial nerve involvement and vasculitic CNS involvement

The third laboratory item requires two of the following three items—reduced serum C4, positive serum rheumatoid factor and positive serum M component.

The main criticism of these criteria has been that these cannot be applied to the patients with negative serum cryoglobulins. However, it has been agreed that if cryoglobulins have been documented in the past, cryoglobulin positivity should be considered even in the patients with negative cryoglobulins presently.⁵⁸

MANAGEMENT OF MIXED CRYOGLOBULINEMIA

The disease manifestations may vary from a benign clinical course in most of the patients to severe or life threatening manifestations. Aim of the therapy is to eradicate HCV infection, delete clonal expansion of B cells and deplete the cryoproteins. The treatment of HCV CV on the basis of disease severity is highlighted in Table 2.

Combination therapy of Peg-IFN-alpha plus ribavirin is first line treatment and has been shown to produce complete clinical response and sustained virological response (SVR) in 78% patients.⁵⁹

Severe life threatening manifestations like acute nephritic or nephrotic syndrome, severe skin ulcers, or other major systemic involvement requires aggressive treatment with immunotherapy. In these patients also, anti HCV therapy is either given simultaneously or sequentially, and is an important part of therapeutic strategy. While the concomitant therapy is likely to prevent viral replication, there are concerns of side effects of combining two forms of therapies. Paradoxical worsening of CV manifestations have also been reported with institution of anti HCV treatment which may be prevented with sequential administration.⁶⁰

Some manifestations like peripheral neuropathy may be refractory to all forms of therapies.

Boceprevir and telaprevir, two direct acting antiviral drugs may be useful when there is failure with standard therapy of Peg IFN-alpha plus ribavirin.⁶¹

Persistence or relapse of CV even after clearance of HCV infection should make one suspect and rule out B cell malignancy as B cell lymphomas have been reported in such cases.⁶²

Most anti-inflammatory drugs used for management of other vasculitides like cyclophosphamide have been used for management of CV. However, it has been shown that immunosuppressive treatment has been associated with increased mortality independent of disease activity.⁶³

Rituximab, a chimeric monoclonal antibody directed against CD 20 has been shown to be effective in CV refractory to antiviral regimens.^{64–66} Numerous case reports and case series have documented the safety and efficacy of rituximab in CV.⁶⁷ Rituximab also has a steroid sparing effect and there are reports of patients being treated without, or with very short course of glucocorticoids.^{65,66,68} Rituximab has become the treatment of choice for life threatening manifestations like gastrointestinal vasculitis.⁶⁹ GISC (The Italian Group for the Study of

Cryoglobulinemia) in its recommendations for management of cryoglobulinemia has issued a statement that rituximab should be used in treating patients with severe manifestations and should be preferred over conventional treatment modalities like glucocorticoids, immunosuppressant and apheresis.⁶⁹

Two randomized controlled trials published recently, have shown the efficacy of rituximab as compared to conventional therapy.^{70,71} Role of expansion of T regulatory (Treg) cells with subcutaneous IL 2 injections and associated clinical improvement in patients with refractory HCV associated CV may suggest that low dose IL2 may promote tolerance but we will have to wait for further studies.⁷²

In future, other anti B cell targeted therapies like ocrelizumab and ofatumumab (anti CD20), epratuzumab (anti CD22) and belimumab (anti BAFF) might also prove useful in management of severe systemic/refractory manifestations.

CONCLUSION

There is causal association between hepatitis B with classical polyarteritis nodosa and hepatitis C with cryoglobulinemic vasculitis. There has been improvement in the understanding of pathogenesis and availability of therapeutic modalities for these vasculitides in recent times. Early identification and prompt institution of appropriate therapy can yield gratifying results.

CONFLICTS OF INTEREST

All authors have none to declare.

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