PLASMAPHERESIS FOR CHRONIC HEPATITIS

Voinov V.A.

I.P. Pavlov First Saint-Petersburg State Medical University, Russia.

Abstract

Presents an analysis of the literature on the mechanisms of formation of chronic hepatitis of virus and toxic nature, which are based on autoimmune processes. There is showing convincing rationale for plasmapheresis in the treatment of these diseases.

Key words: chronic virus hepatitis, plasmapheresis.

Chronic hepatitis B is one of the most severe types of autoimmune diseases. It is known that after the acute hepatitis B chronicity occurs in 5-10% of patients, and according to U.S. statistics in the U.S. the number of patients with chronic hepatitis B was 1.25 million people. At the same time, deaths from chronic hepatitis B in 5 to 10 times higher than from acute, entering the top ten causes of death, 50 times greater than the frequency of deaths of HIV infection [31].

On the scale of the Earth are infected with hepatitis B virus more than one third of the population (approximately 1 billion people) and about ¼ of them will develop chronic hepatitis, cirrhosis and primary liver cancer. Thus 2.1 million people die annually. In Europe, each year 1 million people are infected, of which about 90,000 will be chronically ill and 22,000 will die from cirrhosis or cancer [129].

Chronic forms of hepatitis C in the United States affects about 4.5 million people [63, 80], and in Russia, even their number reaches 10 million people. In St. Petersburg, there are such patients, about 200,000 people (i.e., 4-4.5% of the total population) [90]. Its effects are more severe because the hepatitis C virus (HCV) has the highest chronicity potential being the main reason for the formation of the whole group of chronic liver disease – chronic hepatitis, cirrhosis and hepatocellular carcinoma [85, 108]. From liver disease caused by hepatitis C virus in the United States die each year more than 8,000 people [92]. Across the Earth by patients with hepatitis C (170 million people), there are much higher than in AIDS patients (40 million people), despite the fact that this hepatitis is the same incurable disease [37].

The examination of 20 people 18 years after their accidental exposure to HCV donor plasmapheresis center in the city of Salzburg, it was found that 90% had evidence of chronic HCV infection, 50% had progressive chronic hepatitis and 20% – cirrhosis [25].

Hepatitis D virus also always leads to chronic [109]. Unfortunately and frequency transformation in hepatic carcinoma, although in 20-30 years from the onset of the disease is close to 100% [104].
Hepatitis G virus still poorly understood. It occurs in 1.6% of blood donors, and 20% of drug addicts and patients after multiple blood transfusions [16].

What are the causes of such chronic viral hepatitis? There is much evidence that viral infection, no matter how difficult or, alternatively, it may easily course, causing a cascade of immune-pathogenicity reactions, leading eventually to the formation of autoimmune hepatitis [45, 62]. Confirming the autoimmune nature of chronic hepatitis (especially infection with the hepatitis C virus) is almost regular its combination with other types of autoimmune disease – vasculitis, glomerulonephritis, cryoglobulinemia, polymyositis, pulmonary fibrosis, porphyria, uveitis, keratitis, thrombocytopenia, etc. [20, 22, 87, 93, 117, 122]. In particular, in the genesis of renal lesions leading consider circulating immune complexes containing antigen C [98]. Even after liver transplantation when immunosuppressive therapy helps build-level viremia HCV, symptoms may recur and nephrotic syndrome also [82].

HCV infection is often accompanied and cutaneous manifestations also, such as pruritus, urticaria, porphyria, lichen planus. In addition, these dermatoses long time can be the only manifestations of the underlying disease [38]. In patients with hypertrophic cardiomyopathy symptoms HCV-infection detected much more frequently than in the control groups (15.7% vs. 2.4%) [65]. Since HCV is lymphotrophic, it can be a trigger of clonal B-cell proliferation. Indeed, markers of hepatitis C are often found in non-Hodgkin B-cell lymphoma. On the other hand, the toxic effects of chemotherapy at this type of lymphoma are also the most severe with concomitant chronic hepatitis C [118].

Patients with chronic hepatitis C is often found autoantibodies – rheumatoid factor, an antithyroid immunoglobulin, antinuclear and other mitochondrial antibodies [7, 9, 21, 35, 49, 68, 124]. Cryoglobulinemia accompanies chronic hepatitis C in 36-45%. It has been suggested that this viral infection "starts" and mechanisms of autoimmune hepatitis also [119]. One-third of such patients show autoantibodies to specific human hepatic lipoprotein [28].

HCV viral infection is involved in the pathogenesis and mixed cryoglobulinemia, both through direct formation of immune complexes, leading to vasculitis and exciting lymph-proliferative processes underlying this disease. This is associated with a particular lymphotropism HCV and may also be responsible for the transformation of mixed cryoglobulinemia in malignant lymphoma. HCV-infection apparently also involved in the pathogenesis of idiopathic B-cell non-Hodgkin's lymphoma in the same pathogenic mechanisms [128]. At the same time, cryoglobulinemic vasculitis may be accompanied by multiple fingers necrosis and in the treatment of this complication plasmapheresis finds its application [72].

Anti-HCV antibodies can be detected in 72% of patients with "autoimmune" hepatitis, 50% of patients with alcoholic hepatitis, 66% of drug addicts and in 2.4% of healthy individuals. In
addition, 21.3% for HBsAg positive patients with chronic hepatitis were positive and HCV-viruses, which means more significant than you might think, the spread of this kind of viral infection [95].

By the way, the development of autoimmune mechanisms, only a lesser severity, described also in some other viral infections (hepatitis B and D, herpes simplex-1, Epstein-Barr virus), but only hepatitis C acquire self-progressive malignant nature [108].

It was established that interferon is widely used in the treatment of viral infections may even induce autoimmune processes and cause exacerbations in 4-19% of patients [58, 59, 87, 123]. On the background of interferon in these patients showed a twofold increase in the frequency of formation of autoantibodies to human hepatic lipoprotein, antinuclear and mitochondrial autoantibodies [43]. Interferon possesses cardiotoxicity and can trigger the development of pericarditis [86]. Interferon may contribute to ischemic retinopathy, retinal hemorrhages, optic neuritis, keratoconjunctivitis, uveitis, sometimes with loss of vision [23, 73, 75, 78, 97, 100, 127].

Moreover, in patients with autoimmune predisposition interferon can trigger the development of autoimmune thyroiditis [71], the defeat of the eye muscles, chronic inflammatory demyelinating polyneuropathy and multiple sclerosis [24, 64, 66, 77, 87, 113]. Y. Kato-Motozaki et al. [48] described the formation of heavy polyradiculopathy with the advent of anti-ganglioside antibodies in the treatment of hepatitis B using interferon-alpha, which was stopped only after a course of cascade plasmapheresis. In the experiment on mice application of γ-interferon animal skin causes the formation of antinuclear (anti-DNA) autoantibodies, which were postponed in the vessels of the glomeruli of the kidneys and lead to severe proliferative glomerulonephritis [99]. K.-P. Meyer [69] explicitly states that the use of interferon in patients with autoimmune hepatitis may lead to severe course and even death.

Among the factors that trigger the formation of autoantibodies, are cytokines IL-1β and TNF-α that often present in the formulations of interferon-α and can stimulate an autoimmune disorder with interferon. Their level increases even when vaccination against viral hepatitis A and B, as well as against staph, proteus and Pseudomonas infection. There are also reports of no effect of interferon-α in concomitant HCV- and HBV-infection [128]. Many patients can not tolerate interferon therapy because of the large number of side effects [92]. In particular, reported a significant increase in levels of total cholesterol, triglycerides, very low density lipoproteins, while reducing high-density lipoprotein in the treatment of interferon-α [32, 94, 126]. Other side effects of interferon describe cutaneous manifestations (skin dryness and itching, erythema, seals, reversible alopecia, psoriasis and provocation Herpes labialis) [30].
S. Kiefersauer et al. [51] reported that the HCV-infection, at least 50% of patients remain chronically infected. IFN-α therapy was effective in only 25% of patients with HCV. Assuming that the CD8+ T-cells prevented the therapeutic effect, they have involved the incorporation of monoclonal antibodies to CD8+, leading to a high ratio CD4+/CD8+ from 1.6 to 3.0 during treatment with a gradual decline to 2.3 after 1 year following the last infusion of monoclonal antibodies. In these patients gradually decreased ALT and clinical improvement occurred, which α, β and γ could not be achieved by interferon. HCV have multiple genotypes, with genotype 1b is the most chronicity and it is more resistant to interferon [10]. Even more modern concomitant therapy with INF-alpha-2a and ribavirin does not always lead to success, especially in elderly patients [44, 125]. More than half of patients with chronic hepatitis C are insensitive to interferon [42]. And in general, P.L. Almasio et al. [6] believed too exaggerated the positive effect of such treatment in viral hepatitis C.

On the other hand, should take into account the enormous cost of an intensive course of treatment with interferon, which can reach $ 10,000 [11, 52] and in UK hospitals – up to £ 3,000 with a total maintenance cost £ 93,000 [41]. Based only on clinical and laboratory criteria for chronic hepatitis C is virtually indistinguishable from autoimmune hepatitis [110]. It must be borne in mind that the absence of antinuclear or antibodies to smooth muscle does not exclude the presence of autoimmune hepatitis. That is why we must be careful in appointing interferon for hepatitis C patients who have not excluded autoimmune hepatitis [15]. At the same time, as in chronic hepatitis C can never exclude its autoimmune character, it becomes clear high risk of interferon in such cases.

However, the classical approach to the treatment of such patients as having autoimmune pathology with chronic hepatitis C may result in an increase in virus replication with the risk of deterioration of the clinical course [8, 19].

There is a serious clinical dilemma – both interferon and corticosteroids almost impossible to use. However, only plasmapheresis is a decent alternative antiviral therapy for hepatitis C [87]. Removing autoantibodies plasmapheresis helps restore reparative possibilities of hepatocytes, and, on the other hand, removing the "toxic press" from the immune system should stimulate its normalization.

In recent years, more widespread acquire liver transplantation for chronic hepatitis, cirrhosis and liver tumors. However, even after such operations HCV persists, leading to relapse of chronic hepatitis in 50-60% of patients. Three-month course of ribavirin promotes normalization of aminotransferase levels and histological improvement, but after the cessation of such therapy biochemical signs of hepatitis return again, indicating that the inability even of ribavirin prevent the progression of fibrosis in patients with autoimmune hepatitis C [13, 18].
Intrigue HCV-infection is prolonged "light gap" from infection to clinical manifestations of liver disease – up to 10-20 years. However, such "asymptomatic" is quite relative. Indeed, may not hyperbilirubinemia and signs of portal hypertension. However, careful analysis of these patients reveals a less optimistic picture. In such patients, a significant fatigue observed in 78%, depression in 53%, joint pain – in 53%, weakness – 51%, a sleep disorder in 51%, abdominal discomfort – 51%, weight loss in 43%, headaches – 39%, itching in 39%, ikterus in 20% cases. This suggests that these patients have a significant deterioration in the quality of life, which contradicts the common opinion that chronic hepatitis is virtually asymptomatic until signs of cirrhosis [3]. It is possible that such practices contribute to the above other autoimmune related diseases, are also still in the subclinical phase.

Nevertheless, we must not forget that in the coming years, millions of carriers of hepatitis C virus become seriously ill with a sharp increase in mortality from chronic hepatitis and cirrhosis.

All the above facts convincingly prove autoimmune nature of chronic hepatitis, almost naturally developing after suffering the viral hepatitis B, C and D, and if so, it only plasmapheresis helps to mitigate its manifestations and postpone the inevitable outcome. This raises the question of the appointment of preventive courses of plasmapheresis in the very early rehabilitation period after acute viral hepatitis (especially C and D), as there is no guarantee that will avoid chronic process. Because the occurrence of autoantibodies is provoked both the viral infection, and the changes in the antigenic structure of hepatocytes, which occurred at the height of the disease. "Random" HCV detection must also raise the question of holding such preventive courses of plasmapheresis. Given the same factual incurable viral infection of this kind, even when 10-20 years asymptomatic develop signs of chronic hepatitis B, it is necessary to repeat such courses of plasmapheresis at least once a year for the rest of life [121].

E.G.Kirillova et al. [53] reported positive results of the use of plasmapheresis in the treatment of patients with chronic hepatitis. On the background of improving overall observed decrease in the levels of bilirubin, ALT, circulating immune complexes, alkaline phosphatase, middle weight molecules. Repeated courses of plasmapheresis provide more long-term remission.

B.N.Levitan et al [53] in 56 patients with chronic hepatitis and 20 patients with liver cirrhosis on the background activity of the pathological process and cytolytic syndrome also with courses of plasmapheresis achieved positive results. Improved mood, decreased fatigue and arthralgia, yellowness, itchy skin, decreased level of average weight molecules, antibodies to endotoxin, catabolism products of cellular receptors, bilirubin and ALT, bile acids, alkaline phosphatase, and significantly reduced the concentration of cytokine such as tumor necrosis
factor (from 121.6 to 69.3 pg/ml). There are disposed fibrin monomer complexes, and other degradation products of fibrinogen.

V.G.Radchenko et al. [88] sessions of plasmapheresis combined with extracorporeal laser (HeNe) blood irradiation and external exposure of the liver. A.G.Olsansky et al. [79] showed that plasma cryoprecipitate obtained from patients with hepatitis C, a few orders of magnitude higher content RNA HCV, than native plasma. This allowed advantageously make use of this technique in treating hepatitis C.

Positive results were obtained using a lectin affinity plasmapheresis with cartridges, resulting in a significant reduction in HCV-viremia [114]. In cases of advanced chronic hepatitis C with the development of hepatic encephalopathy plasmapheresis also contributed to the improvement of overall health and eliminate the symptoms of intoxication with a decrease in the levels of bilirubin and transaminase almost back to normal [103].

However, liver transplant patients with chronic hepatitis C does not eliminate the prospects injury donor liver. Moreover, often the development of cirrhosis in the transplanted liver is more intensive than before transplantation [27]. In such cases, M. Tanguchi et al. [112] used a cascade plasmapheresis method by which not only selectively removed autoantibodies but do complex HCV therapy (interferon, ribavirin, including cascade plasmapheresis), HCV RNA caused a reduction to 8.2% and 0.7% on the 5th and 30th days of treatment, respectively. In three patients, to whom such therapy was carried out as a preventive measure, did not show recurrence of the disease even one year after treatment, and the patient who has already developed signs of fibrous cholestatic hepatitis has been rapid inverse dynamics transplanted liver lesions. Such as a sharp decline in the amount of hepatitis C virus in the blood (and without the additional use of antiviral drugs) using cascade plasmapheresis have A. Ramunni et al. [91] and N. Hanafusa et al. [40]. Cascade plasmapheresis was used for the purpose of viral decontamination and in patients who have previously undertaken therapy with interferon or its combination with ribavirin was unsuccessful [52]. It was demonstrated its effectiveness also the method of lectin affinity plasma adsorption, which allowed 14-fold lower content of HCV [115].

In chronic hepatitis alcoholic genesis plasmapheresis courses also contribute to stabilization with decreased levels of bilirubin, ALT, alkaline phosphatase, and a decrease in liver size by ultrasound. In the future, the application of hepatic protectors and a diet (excluding alcohol) possible to achieved sufficiently stable and long-term remission [33, 102].

We should also note the leading role of chronic alcohol intoxication in the development of both primary chronic hepatitis and alcoholic cirrhosis. Moreover, there is evidence that chronic alcoholism develops immunosuppression with suppression ability to combat hepatitis, contributing to a more severe course of illness and chronicity [34]. Found that drinking more
than 90 g of alcohol per day, significantly increasing the severity of chronic hepatitis [10]. This underlines the need for abstinence all kinds of alcoholic beverages in already developed chronic liver disease and even in those cases when you can expect a high probability of such process in HCV- infected individuals.

But against the background of developing cirrhosis with severe chronic liver insufficiency courses of plasmapheresis and cryo-plasmasorption also contribute some stabilization of the patients [83, 88, 101]. Thus, according to B.V. Stukov et al. [111] in these patients as a result of the treatment of hepatic it was stoped encephalopathy phenomenon, decreased ascites, decreased level of cholestasis, and prothrombin index rose more than 60%. Partial reimbursement of plasma after cryo-treatment helped stabilize the level of total protein in the blood. Plasmapheresis also helps in alleviating itching which often accompanies cirrhosis, for up to 6 months [69].

A.N. Plotsky et al. (2003) in liver cirrhosis complicated by diuretic resistant ascites plasmapheresis was performed, and as a replacing solution, they used ascites derived with paracentesis, which was subjected to ultrafiltration and cryosorption. It restored the blood circulating volume, reduced protein loss, reduced the CIC, bilirubin and transaminases level. In extremely severe hepatic insufficiency positive results obtained using the system MARS, when the plasma obtained by membrane plasmapheresis further passes through a special column, wherein the albumin adsorbed related toxins are then removed by dialysis, and then returned to the patient a purified [50].

The same positive effect was obtained also cryo-apheresis at hepatic failure [46]. Shin Hwang et al. [105] reported the case that after removal of the right lobe of the liver for primary hepatocellular carcinoma on a background of already developed cirrhosis of the liver due to hepatitis B the manifestations of cirrhosis increased with the accretion of ascites, but plasmapheresis sessions allowed the restoration of liver function and reduce portal hypertension at the significant period.

And may experience a "primary" autoimmune hepatitis – chronic progressive necroinflammatory liver disease as a result of autoantibodies: to a specific hepatic lipoprotein, antinuclear, anti-smooth-muscles, anti-neutrophil cytoplasmic, and several others. It occurs in both adults (mostly women) and children [14, 70]. Autoimmune hepatitis, as mentioned above, may occur as a result of interferon-treatment of viral hepatitis [55]. Plasma exchange allow in 85% of cases to improve the overall condition of the patients and significantly reduce the level of bilirubin, ALT and AST in remission up to 10 months [54].
**Chronic alcoholic hepatitis and liver cirrhosis** – occur as a result of the formation of free radicals under the action of ethanol to damage cell membranes and organelles. Oxidation product of alcohol – acetaldehyde – also highlights the free radicals. Alcohol promotes the release also of cytotoxic cytokine (IL-1, IL-6, IL-8, TNF-α). Increasing the number of cytotoxic T-lymphocytes in the liver, promote the development of necrosis and fibrosis, and later cirrhosis also. In addition, alcohol contributes to the progression and other forms of chronic form of chronic hepatitis.

It may be development of chronic hepatitis and in some metabolic disorders involving the accumulation and deposition of copper in the liver and brain in Wilson-Konovalov disease. There may be different degrees of liver damage, up to fulminant hepatic failure. Cerebral manifestations are characterized by rigid-hyperkinetic symptoms. There are perhaps the development of hemolysis with hemolytic anemia, hemolytic jaundice, thrombocytopenia and leukopenia. Used in the treatment of this disease chelates (D-penicillamine, kuprenil) have hepato- and nephrotoxicity and often lead to serious complications. Plasmapheresis helps to reduce the copper content in the body and to stop developing complications [107].

Close pathology is idiopathic hemochromatosis, accompanied by the accumulation of iron. Efferent therapy in these cases may also be useful, and in this case more effective removal of iron-containing red blood cells, ie, regular bloodletting [69].

**Drug induced hepatitis** is a form of iatrogenic illnesses. Essentially there is no medication that would not cause damage to the liver [116]. Protein P450 system in the metabolism of drugs contributes to the formation of toxic metabolites. Pregnancy increases the risk of drugs toxicity.

**Exogenous toxic hepatitis**, often develops when receiving such a tuberculosis drug *isoniazid*. Especially dangerous is the combination of the latter with rifampicin. Evolving with hepatocyte necrosis accompanied mortality is 10 times greater than in viral hepatitis. Although rare (1 in 10,000 anesthesias), but may develop severe liver damage as a result of inhalation of halothane. Even such a "harmless" drug like paracetamol, at doses above 10 g can cause necrosis of hepatocytes fatal [69]. Described the development of severe acute hepatitis also omeprazole used in the treatment of hyperacidity gastritis [76].

Hepatotoxic are many anticancer drugs – methotrexate, anthracyclines, as well as a number of other drugs (*allopurinol, coumarin, diclofenac, methyltdopa, minocycline, fentoin, sulfosaltsil*). At the same degenerative processes in the liver can lead to the development of cholestasis and veno-occlusive disease of the liver [1, 26, 39].

Liver damage as a result of receiving hepatotoxic drugs almost never passed unnoticed. P.G.Aithal and C.P. Day [4] when examining these patients, 40 years later revealed yellowness in 24, abnormal liver function tests in 17 and renal failure in 3 patients. The main reasons were
antibiotics (13) and non-steroidal anti-inflammatory drugs (11). Initial histological studies revealed acute hepatitis in 6, chronic hepatitis in 20 and 18 patients with cholestasis.

These data also underscore the advisability timely excretion of these hepatotoxic drugs to reduce the scale of defeat and prevent the progression of pathological disorders of the liver.

**Primary biliary cirrhosis** – a chronic, progressive autoimmune cholestatic disease. Occurs mainly in middle-aged women with a frequency of 3.9 - 15 per 1 million population. At this disease occurs degradation small intralobular bile ducts with the transition fibrosis and cirrhosis with portal hypertension development. Manifested yellowness of the skin, weakness, persistent pruritus, osteoporosis, hypercholesterolemia with xanthomas and xanthelasma [56]. At laboratory monitoring revealed marked cholestasis with increased levels of bilirubin, transaminases, immunoglobulin M, detect antibodies against mitochondria.

Important role in the pathogenesis of oxidative stress plays a significant accumulation of free radicals, malondialdehyde and 8-isoprostane due to lower antioxidant activity, vitamin A and selenium [2, 36].

As a leading etiological factor of the disease is also accumulation of autoantibodies, the substantial assistance to patients may have plasmapheresis [5, 12, 54]. Indeed, as a result of the plasmapheresis course total bilirubin decreased by 25-30%, ALT and AST – by 12-15%, and normalized levels of CIC and medium-sized molecules, which helped to reduce the itching and asthenoneurotic manifestations [4].

Close to this liver disease also is **primary sclerosing autoimmune cholangitis**. In this high-frequency detected antinuclear autoantibody [81].

Patients with autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis can find a whole range of autoantibodies: antinuclear (ANA), anti-smooth muscle (SMA), mitochondrial (AMA), anti-neutrophil cytoplasmic (ANCA), intestinal antibodies anti-ribosomal antibody (ARA) [67, 84, 106]. Sclerosing cholangitis is often accompanied by IgG4-antibodies with infiltration of T-lymphocytes and the concomitant development of cholecystitis, retroperitoneal fibrosis, tubulo-interstitial nephritis, interstitial pneumonia, prostatitis, and lymphadenopathy [47].

Often, development and combinations of autoimmune hepatitis with primary biliary cirrhosis and primary sclerosing cholangitis, and sometimes with ulcerative colitis and Crohn's disease [60, 74, 96].

In all such cases efferent therapy also helps to smooth the general toxic effect, as in the development of acute hepatitis, and chronic exposure to toxicants hepatotropic.
**Budd-Chiari syndrome** occurs more frequently in antiphospholipid syndrome and is characterized by progressive obstruction of the hepatic veins from the lobular vein to the confluence of the inferior vena cava into the right atrium. Manifested hepatomegaly, abdominal pain, ascites. Can occur acutely and malignant, but mostly for its chronic and asymptomatic. In the latter case, there is an insignificant increase of the liver by increasing the background activity of transaminase and alkaline phosphatase in conjunction with hypoalbuminaemia. Nevertheless, such a chronic metabolic disorder of the liver cells leads to fibrosis and cirrhosis [29].

Autoimmune nature of the disease involves the use of plasmapheresis to remove antibody as vaso-active and pathological metabolites. Thus S.V.Varlamova et al. [120] performed an intensive course of plasmapheresis in the treatment of acute proceeds Budd-Chiari syndrome with obstruction of blood flow in the hepatic veins and rapid progression of ascites and oliguria due to high levels of AST (796 u/l), ALT (512 u/l), LDH (7489 u/l), and bilirubinemia. After three plasma exchange procedure was then repeated 2-3 times a week with the removal of up to 0.5 CPV. Total patient was 11 plasmapheresis procedures with removal of 11,850 ml of plasma (4 CPV), and substitution of fresh frozen plasma. As a result, the treatment of positive dynamics – reduction in liver size and ascites with incomplete recanalization of two hepatic veins.

**References**


