REVIEW ARTICLE

Mixed cryoglobulinemia associated with chronic HCV infection in the era of modern antiviral therapy: Can the problem be considered solved?

(Literature review)

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Abstract

Mixed cryoglobulinemia is the most common extrahepatic manifestation of chronic HCV infection. The disease can occur both asymptomatically and in the form of systemic vasculitis with a wide range of clinical manifestations.

The development of cryoglobulinemia is based on relatively benign lymphoproliferation, which, as pathological clones increase and their malignancy can lead to the appearance of B-cell non-Hodgkin's lymphomas. The new treatment of HCV infection with direct acting antivirals allows to achieve an increase in the rate of virus elimination. However, the clinical and, especially, immunological responses associated with the disappearance of cryoglobulins, as well as the normalization of the rheumatoid factor and C4 complement components, were significantly weaker compared to the virological response. Recently, it became known about the possible positive dynamics of these parameters in the future course, but the timing and volume of such observations are clearly insufficient. The persistence of elevated rheumatoid factor values, hypocomplementemia, and, especially, cryoglobulinemia after achieving a sustained virologic response as a result of antiviral therapy raises a number of serious questions relevant for clinical practice. Among the main issues are how often and how quickly normalization of these immunological disorders is possible? What are the consequences of their persistence? Under what conditions is it appropriate to consider alternative approaches to antiviral therapy and to use immunobiological drugs aimed at suppressing B-lymphocyte proliferation?

These problems, as well as some aspects of the pathogenesis, clinical course, and treatment of extrahepatic manifestations of chronic HCV infection based on virus-induced lymphoproliferation are discussed in this literature review.

Key Words: chronic HCV infection, mixed cryoglobulinemia, cryoglobulinemic vasculitis, direct acting antivirals.

Hepatitis C virus (HCV) causes chronic liver disease and its complications as well as severe disorders: mixed cryoglobulinemia with systemic vasculitis, B-cell non-Hodgkin lymphoma, glomerulonephritis, thyroiditis, papillary thyroid cancer, insulin resistance, type 2 diabetes mellitus, the pathology of cardiovasular and other systems[1,2,4,5,6].

Mixed cryoglobulinemia (MC) is the most frequent extrahepatic manifestation of chronic HCV infection, which develops, along with B-cell non-Hodgkin's lymphoma, due to viral tropism to not only to hepatocytes, but to B-lymphocytes as well[7,8,9].

The high efficiency and safety of modern direct acting antivirals (DAAs) have opened a new era in the treatment of chronic HCV infection, its complications and extrahepatic manifestations, including those based on lymphoproliferative processes.

The purpose of this review is to analyze the impact of modern antiviral therapy on the course and outcomes of the MC associated with the chronic HCV infection.

A distinctive feature of cryoglobulinemia is the production of specific abnormal proteins - cryoglobulins (CG), which can precipitate when cooled and dissolve when subsequently heated to the body temperature.

Depending on the CG structure, according to the currently adopted classification, there are three types of cryoglobulinemia[10]. Of these, types II and III represent MC variants: type II is characterized by the presence of monoclonal IgM with the rheumatoid factor (RF) activity and polyclonal IgG, whereas type III is formed by polyclonal IgM with the RF activity and polyclonal IgG. In 80-90% of cases, the development of type II cryoglobulinemia is associated with the chronic HCV infection, whereas type III is more common in autoimmune diseases[11,12,13].

The incidence of the MC among HCV patients is known to range between 25 to 60%, while its clinical manifestations, cryoglobulinemic vasculitis (CryoVas) in particular, are observed only in 5-15% of patients [13,14,15,16,17]. The MC is more common in Southern Europe residents compared to Northern Europe, North America and Asia[18,19,20.21]. The reasons for this uneven distribution are not clear and may be related to genetic features or environmental factors. Clinically manifesting MC is more likely to develop in the elderly with a longer HCV infection course and a higher cryocrit level[21].

Pathogenetic mechanisms and clinical manifestations

Mechanisms of the MC and CryoVas development include both direct and indirect activation of B-lymphocytes by viral particles. In the first case, virus affects B-lymphocyte through its surface protein E2, binding to it with a specific CD81 receptor which complexes with CD19 and CD21. This circumstance, as well as the interaction of viral particle with another B-cell receptor (BCR), leads to a decreased B cells activation threshold[22]. In the second case, B-lymphocytes are stimulated by their activation factor (BAFF) which is produced by the cells of inflammatory infiltrate in portal tracts as a result of a contact with virus or viral core protein[22]. Hepatocytic miR-122 production with its spread through the systemic circulation, as well as co-stimulating B 7.2 (CD86) receptors expression on B-cells also contributes to B-clones activation under the influence of HCV[23].

Remaining open is a question of priority in the pathogenesis of lymphoproliferative and immunopathological processes leading to the development of

CryoVas and B-cell non-Hodgkin's lymphoma: intracellular viral replication in B cells or their prolonged stimulation by virus and its proteins[24,25,26]. It seems that the intracellular presence of viral proteins through the production of nitric oxide synthase (NOS) induces DNA damage and subsequent mutations in tumor suppressor genes (p53, BCL-6, β-catenin). It is assumed that the HCV replication in B-lymphocytes contributes to the emergence of an antiapoptotic phenotype due to IL10, IL2, BCL-2 overexpression, as well as caspases 3/7/9 suppression[22]. It was also has been stated that the probability of developing the MC, and possibly the B-cell non-Hodgkin's lymphoma in chronic HCV infection is increased in those with CD5+CD20 dim phenotype ("CLL-like" variant)[27].

It is known that in the process of B lymphocytes clonal expansion, VH1-69 cells predominate, which play an important role in the production of IgMs with RF activity. The latter, when combined with IgGs and viral particles or "core" proteins, form the immune complexes capable of cryoprecipitation. These complexes activate the complement system via C1q component by classical route, and are deposited in small-to medium-sized vessels, binding to C1q receptors on endothelial surface. Complement system activation provides leukocytes and monocytes chemotaxis, which make a decisive contribution to vasculitis development[28].

The range of various organs involvement in the case of the CryoVas is quite wide. The clinical manifestation is determined by the localization of the affected vessels. The course of CryoVas differs in a significant variety – from relatively benign to rapidly progressing forms[28,29,30,31]. The prognosis of CryoVas has been considered quite serious until recently, with 5-and 10-year survival rates being 75% and 63%, respectively[32,33].

The most severe CryoVas form develops in the presence of advanced vascular lesion, being a life-threatening condition. In such vasculitis course, the gastrointestinal tract may be involved in the pathological process, with hemorrhages as a result of damage to mesenteric vessels; the lungs may be affected in form of hemorrhagic alveolitis and interstitial pulmonary fibrosis; the heart is impaired in form of coronariitis, with possible myocardial infarction, pericarditis, dilatation cardiomyopathy, and heart failure[12,32]. It is also important to emphasize that in the MC associated with chronic HCV infection, the risk of B-cell non-Hodgkin's lymphomas is 35 times higher than in general population[34]. In milder cases, the CryoVas can manifest as damage to individual organs and systems. In this case, the most commonly involved in the process are the vessels of the skin, kidneys and peripheral nervous system.

Possibilities of modern therapy

The complex pathogenetic mechanism of MC and CryoVas development involves a multi-vector approach to disease management. Recognizing the priority of antiviral therapy, ever since the use of interferons, in severe cases of the disease not only etiotropic, but also pathogenetic approaches have been widely used[35,36,37]. Plasmapheresis is also recommended for elimination of pathological immune complexes, the presence of which determines the development of vasculitis. The principles of such comprehensive approach were brilliantly illustrated by Saadoun D. et al.[38]. The efficacy of antiviral therapy (AVT) in the treatment of cryovasculitis associated with the chronic HCV infection has been an important argument in favor of the etiological

role of virus. Despite the fact that in the interferon and ribavirin treatment era the HCV elimination rate (both in manifest and asymptomatic MC cases) was lower compared to the rate of uncomplicated chronic HCV infection, achieving the aviremia was associated with the improvements in clinical disease activity in a significant proportion of HCV patients[39]. At the same time, the treatment efficacy of active CryoVas (evaluated by rate and duration of remissions) was lower when using only antiviral therapy, as compared to the AVT combined with CD20 monoclonal antibodies (rituximab). In particular, Dommacco F. et al. found that complete clinical response and stability of the CryoVas remission at 24 months after antiviral monotherapy were 33% and 40%, respectively, compared to 54% and 83% after a combined therapy regimen[35]. Furthermore, Saadoun D. et al. demonstrated that the inclusion of rituximab in the scheme had made it possible to reduce the activity of such a difficult-to-treat CryoVas component as glomerulonephritis which occurs in 20-30% of cases[37,40]. Another important result of the treatment with the AVT and rituximab combination was a statistically significant reduction in the proportion of VH1-69 B-cell clones which, as mentioned above, play an important role in the MC development. In turn, the treatment efficacy of monoclonal antibodies alone was lower compared to the combination scheme, but the differences were not statistically significant. This may have been due to a small sample size of the studied patient groups[33]. There is an interesting experience of using low doses of rituximab in CryoVas patients with previous AVT failure[41]. Two 250 mg/m^2 doses of drug with a week interval were not inferior to the conventional treatment regimen.

A comprehensive approach to the CryoVas treatment also includes the use of traditional immunosuppressive drugs, such as corticosteroids and cytostatics, and/or plasma exchange. The use of immunosuppression and the elimination of cryoglobulin complexes is particularly important in the early treatment stages of aggressive vasculitis forms, since monoclonal antibodies have a delayed effect.

As DAA-based regimens have been implemented in clinical practice, a new era in the treatment of chronic HCV infection has begun. This scheme allowed to abandon the use of interferon with its frequent and severe adverse effects, significantly increasing the efficacy and safety of treatment[42]. An efficacy criterion of modern AVT is the achievement of a sustained virological response, which means that virus elimination persists for 12 or more weeks (SVR12) after the treatment discontinuation, provided that highly sensitive HCV detection methods are used[43, 44].

The use of these drugs made it possible to achieve the SVR12 in 95-100% of cases of uncomplicated chronic hepatitis C[40,45,46]. Over the past years, a certain experience has already been accumulated in the DAAs treatment of chronic HCV infection patients with extrahepatic manifestations, including the CryoVas.

One of the first studies to assess the efficacy of the DAA-based regimens was VASCUVALDIC where the results of a 24-week treatment of 24 CryoVas patients with the combination of sofosbuvir and ribavirin were analyzed[15]. The SVR12 was stated in 74%. Two patients were non-responders, four others had a relapse of viremia. Notably, the study group included predominantly HCV genotypes 1 (50%), as well as 4 and 5 (17%), in which the administration of sofosbuvir/ribavirin combination could not be

considered optimal. The vasculitis clinically presented with purpura and peripheral neuropathy in 2/3 of patients; with arthralgia – in slightly more than 1/2 of patients, with glomerulonephritis – in 1/5, and with skin ulceration – in 12% of cases. Advanced hepatic fibrosis (F3-F4) was detected in 58% of patients. In addition to AVT, only 7 (29%) patients received various immunosuppressive therapies (prednisolone, cyclophosphamide) ± rituximab and/or plasma exchange. At the same time, a complete clinical remission (which means a decreased severity of all clinical manifestations of vasculitis), was achieved in 87% of patients. Immunological parameters improved to a lesser extent – cryoglobulins disappeared only in 42% of cases.

In the study of Sise E. et al., 12 patients received sofosbuvir-containing regimens. In 6 cases, the antiviral therapy was preceded by a combination of prednisolone, rituximab and plasma exchange[47]. The SVR12 was achieved in 83% of patients, and immunological response (negative cryoglobulin test) – only in 44% of patients. In all patients with glomerulonephritis, proteinuria retained, although with a tendency to decrease.

A weaker immunological response was detected in the Canadian population[48]. Though out of 17 CryoVas patients who received the DAAs 15 (88%) achieved the SVR12, the elimination of cryoglobulins was observed in only 4 (27%) cases. At the same time, in asymptomatic MC, the SVR12 was detected in 44 out of 48 (92%) patients, and the elimination of cryoglobulins was observed in 23 out of 48 (54%) patients.

In our follow-up of 25 HCV-infected patients (8 with asymptomatic MC, and 17 with the CryoVas), the SVR12 after 24 weeks of treatment with the combination of daclatasvir and asunaprevir (patients with 1b HCV genotype), or daclatasvir and sofosbuvir (in those with 3b HCV genotype) was 96%. Cryoglobulins elimination, as in the previous study, occurred only in 29% of patients[49]. According to Obrișca et al., in a group of 67 patients, persistent cryoglobulinemia at SVR12 100% was also detected in almost 1/3 of cases[40]. At the same time, 19 of 22 patients without renal disorders developed a complete, and 3 patients - partial clinical remission. In 2 of 9 patients with cryoglobulinemic glomerulonephritis, a complete clinical remission was observed. In 1 case, de novo glomerulonephritis was diagnosed, and in the remaining 6 patients, the symptoms were unchanged or the disease progressed requiring additional immunosuppressive therapy. A similar approach has been used by the other researchers in rare glomerulonephritis remissions after the AVT[50,51]. According to our data, the regression of glomerulonephritis in CryoVas achieved with DAA therapy was observed only in 56% of patients with SVR12[49].

The study of Boglione L. et al. demonstrated that chronic HCV infection patients with the MC who received ribavirin as part of the DAA therapy showed higher rates of clinical and immunological response, which, according to the authors, is associated with ribavirin's immunomodulatory properties[52].

Thus, the use of modern AVT failed to induce a noticeable increase in the rates of clinical and, in particular, immunological responses in the CryoVas, despite the high level of the SVR12[53]. Moreover, according to the International Study Group of Extra-hepatic Manifestations related to HCV (ISG-EHCV), 2016, based on the findings obtained from 120 patients it was shown that a complete clinical response and the elimination of cryoglobulins

were observed less frequently after the AVT with DAAs compared to interferon-containing regimens (68% vs. 76% and 47% vs. 56%, respectively[54].

Immunological disorders after successful HCV elimination

Cryoglobulins persistence in a significant number of patients after a successful AVT course indicates a continued production of antibodies with the RF activity that form a cryoglobulinemic complex even after virus is eliminated from blood. In this regard, clinicians have a number of questions related to the assessment of possible outcome of residual cryoglobulinemia after achieving aviremia due to the AVT. Firstly, what is the likelihood of future disappearance or decrease of cryoglobulin production under these conditions? Secondly, are there any risks of the CryoVas exacerbation and B-cell non-Hodgkin's lymphoma development? Thirdly, are there any predictors of the malignant transformation of the lymphoproliferation process? Fourthly, in which cases, and at what stage of the disease, it would be advisable to use the agents acting on other CryoVas pathogenesis components, in particular suppression of B-lymphocytes clonal expansion? Finally, taking into account possible viral persistence in immune cells, to what extent can we discuss the feasibility of non-standard AVT regimens while maintaining cryoglobulinemia and high RF levels after the SVR is achieved?

Information is gradually accumulating in literature presents a growing evidence about possible disappearance of CG after achieving aviremia due to the AVT. Back in the era of interferon and ribavirin therapy, Gragnani L. et al. noticed a decreased incidence of cryoglobulinemia in 63 CryoVas patients (from 100% to 3.3%) 6 months after achieving the SVR12[39]. At the same period, the number of patients with a high RF level decreased from 96.7% to 31.1%, and the proportion of patients with an abnormally low level of the complement C4 component reduced from 86.7% to 9.8%.

Using modern DAA-based regimens the same authors, in their study of 44 CryoVas patients after achieving the SVR12 and reducing vasculitis activity by Bermingham scale criteria, showed an improvement in immunological parameters over the next 3 months[55]. For example, level of cryocrit decreased from 2.5% to 1.8%; the proportion of patients without cryoglobulinemia increased from 32% to 39.5%; the RF level decreased from 66.2 IU/ml to 39.0 IU/ml, and the number of patients with a normalized C4 component level increased from 45% to 55%. A similar progression of immunological parameters at the same periods of time was found by Bonacci M. et al.[56]. Later, same authors published study data on a larger clinical material, with the longest to-date follow-up period after the SVR achievment[57]. Thus, 46 CryoVas patients and 42 asymptomatic MC patients have been followed up for 24 months (17;41) after reaching the SVR12. By the end of the study, the incidence of cryoglobulinemia showed a nearly 5-times decrease in both groups; however, cryoglobulins were still detected in 22% of patients. By this time, the immunological response (understood as cryoglobulins elimination and complement and/or RF levels normalization) was observed in 66% of cases in the CryoVas group and in 70% of patients in the asymptomatic MC group. The association between the lower cryocrit (below 2.7%) and a more frequent immunological remission was also demonstrated.

Stubbs A. et al. in 2018 described 2 cases of a long-term (17-24 months) persistence of characteristic changes in the RF and the C4 complement component levels remained, although there was some positive dynamics.

We presented a case report of a patient with a severe long-term HCV-associated CryoVas who was followed-up for 4 years after achieving the SVR12 due to the AVT with the asunaprevir/daclatasvir combination. At the time of SVR24 achievement, her cryoglobulins were no longer detected. However, over the next 4 years, abnormal values of the RF and the C4 complement component still persisted, although a complete clinical and laboratory disease remission was observed[59].

Currently, there is a clear lack of evidence on the frequency, timing and sequelae of recurrent CryoVas, as well as on the possibility of B-cell non-Hodgkin's lymphoma development in the presence of a persistent MC or other inherent immunological disorders after a successful AVT completion.

An early CryoVas relapse after the sofosbuvir and ribavirin therapy was observed by Sollima S. et al.[60]. In this case authors reported the achievement of HCV elimination, as well as the disappearance of cryoglobulins, 12 weeks after the AVT completion. There also was a complete clinical remission of vasculitis, including glomerulonephritis. However, 2 months after the immunization against influenza, the patient developed the CryoVas relapse with skin manifestations, proteinuria up to 1.1 g/day and reduction of kidney function. Cryoglobulinemia was detected again. Over the next 2 months, there was a spontaneous partial regression of purpura and a restoration of renal function to initial levels, although cryoglobulinemia persisted.

A similar scenario was observed by Bonacci M. et al.[57] They presented data on 5 out of 46 patients who developed escalation of vasculitis (4 out of 5 had liver cirrhosis). One of them relapsed 6 months after the AVT completion, others – in a later period (12-23 months). Corticosteroid therapy was required in 2 patients who were diagnosed with nephrotic syndrome and intestinal impairment.

According to Visentini M. et al., the CryoVas relapsed in 4 patients between 1 and 13 months after the HCV elimination. Notably, in 3 of them, respiratory diseases served as a provoking factor, and in 1 patient the CryoVas exacerbation occurred due to a tumor progression[61].

Cases of the de novo cryoglobulinemic glomerulonephritis after a successful HCV treatment are noteworthy. Thus, according to Obrișca B. et al., one asymptomatic MC patient with the disease persisting developed a clinical picture of glomerulonephritis after viral elimination[40]. A similar scenario was observed by Ghosn M. et al., who diagnosed a de novo cryoglobulinemic glomerulonephritis in 2 patients approximately 1 year after reaching the SVR12 (1 patient after the AVT including with the use of simeprevir, and 1 patient after treatment with pegylated INF-alpha, ribavirin, and sofosbuvir)[62].

Thus, despite the successful AVT, cryoglobulins as well as high RF levels and decreased C4 complement component levels remain in some patients. A number of authors state that a persistent immune dysregulation is caused by an altered B-cell phenotype, with an increased amount of IgM+memory B-cells and an imbalance between T-helpers and regulatory T-cells, which, apparently, can support the cryoglobulins production even in the absence of B-lymphocytes viral stimulation[63]. Landau D-A. et al also believe

that the virus necessary for the initiation of transformation and proliferation of B-cellular clones, subsequently loses its significance[64]. It is also assumed that crossing of a certain "point of no return" in the process of lymphoproliferation is likely, after which it loses its antigen dependence[12,14,57,64,65]. It was also noted that B-cell clones expressing a B-cell receptor (BCR) and usually found in the MCG, persist in the peripheral circulation in some patients after virus eradication[65,66], which in the condition of an abundant production can lead to their activation and expansion, as well as to the MCG recurrence after virus elimination.

There is another point of view; it is assumed that IgMk-producing B-cell clones, the "survivors" of virus elimination, eventually lose the ability to produce pathological antibodies. However, under certain conditions this ability can be restored due to adverse factors, such as viral infections, malignancies or vaccination[60,61].

Among other hypotheses of the cryoglobulins persistence after the SVR achievement, it is considered a possibility of the HCV "harboring" in extrahepatic foci (cryoprecipitate, peripheral mononuclear cells), as well as a decreased ability of immune complexes utilization in cases of progressive liver fibrosis[57,67]. In particular, it was shown that in the presence of surviving B-cell clones with 14;18 translocation after a successful AVT, small amounts of viral RNA could have been retained in lymphoid tissue[68,69,70].

In this regard, a clinical follow-up performed by Chowdhury R. and Tsen A. is also of great interest[71]. According to their data, a CryoVas patient who had been treated with corticosteroids and cyclophosphomide, and then DAAs, achieved the SVR12 as well as a complete clinical response and the elimination of cryoglobulins. However, 2 months later, a severe relapse developed with renal impairment, nephrotic proteinuria, hematuria, and an acute kidney injury. The severity of the disease required a re-treatment with rituximab, as well as plasma exchange. An important feature of this case was the HCV RNA detection in cryoprecipitate on persisting viremia. Similarly, other authors also found a higher virus concentration in the cryoprecipitate compared to blood serum[72,73,74,75].

It is long and well known that in the presence of the MCG associated with the HCV infection, there is an increased likelihood of a neoplastic transformation of a relatively benign initial lymphoproliferation until the onset of B-cell non-Hodgkin's lymphomas (NHL). The duration of MC, in addition to HCV, is one of the risk factors. NHL cases were found to be diagnosed in almost 10% of patients in a mean of 6.26 years from cryoglobulinemia detection, regardless of the presence or absence of vasculitis[34,76].

In terms of CryoVas relapses in persistent cryoglobulinemia after a successful AVT, there is a reasonable interest to the possibility of developing the HCV-associated NHL after virus elimination in cases of maintained immunological disorders. There are only a few publications on this issue. For example, according to Landau D-A. et al. in 2 of 8 patients with a relapsed CGV who underwent an effective interferon therapy with ribavirin, the disease exacerbation occured on the background of a newly diagnosed lymphoplasmocytic lymphoma[64].

One of the patients was also diagnosed a kidney damage caused by high cryoglobulinemia level. 3 cycles of the cytostatic therapy allowed the achievement of a stable lymphoproliferative disease remission,

cryoglobulinemia elimination, and renal function improvement. The achieved remission was maintained in the next 3 years of the follow-up. In the second case, a temporary improvement was observed on 2-year corticosteroid and chlorambucil therapy. By the end of this period, there was a severe relapse of lymphoma with a fatal outcome. In the presented cases, the progression of the lymphoproliferative process was diagnosed 2 months after the virus and cryoglobulinemia elimination. In consideration of such a short time period, it seems that cryoglobulinemia and vasculitis recurrence in these patients was most likely due to the previously undiagnosed lymphoplasmacytic lymphoma.

We couldn't find any reports of lymphoma development in the presence of persisting cryoglobulinemia after reaching the SVR, which seems to be associated with a relatively short follow-up period for these patients after the DAA-based regimens had been introduced into clinical practice. In addition, after a successful hepatitis C treatment, many patients might not be monitored for cryoglobulins, and in cases of the NHL detection and further observation by physicians of another specialty, their presence might not have been taken into account.

Under conditions of insufficient data the lack of data regarding lymphomas detection after an effective DAAs therapy in the MC patients, there is an increasing amount of literature reports on good prospects of using the DAAs in cases of the NHL in the HCV-infected patients[77,78,79,80,81]. This information has something in common with the previously reported results of interferon treatment, which evidenced a possible regression of indolent lymphomas associated with chronic HCV infection, without administering chemotherapy, in 75% of patients[82].

Visentini M. et al. has compared treatment results of indolent HCV-associated NHL with interferon-free and interferon-containing regimens. It was shown that, despite a higher SVR rate in the group of DAAs-treated patients (98% vs. 76%), their hematological response after the virus eradication was worse compared to similar patients who underwent interferon therapy (73% vs. 83-96%, respectively)[83].

Also, there were reports on a possible positive effect of antiviral DAAs treatment on the course and outcomes of the HCV-associated NHL with poor prognosis, requiring mandatory specific chemotherapy[84,85]. It's important that a regression or a prolonged remission of the disease, as in the CryoVas cases, was closely associated with the presence of aviremia; hematological response after achieving the SVR in the NHL patients was significantly more common than in those with AVT failure[84].

To date, there is no doubt that the AVT with modern effective and safe DAAs in the HCV-associated MC helps to achieve not only rapid virus elimination with the SVR close to 100%, but also promotes a clinical response in CryoVas patients, with a decreased frequency of cryoglobulinemia and other immunological disorders. However, as previously noted, even in cases of a successful MC treatment with complete clinical remission of vasculitis in the setting of HCV elimination, in a number of patients cryoglobulinemia, abnormal RF and C4 complement component levels still remain. Considering these parameters as a possible indicator of a persistence of pathological B-clones with a potential to activation and progression of lymphoproliferation, the development of novel, non-standard approaches to the adjustment of disease management may be necessary. Taking into

account the possibility of the HCV "harboring" in the extrahepatic foci after the SVR achievement, especially in patients with progressive liver fibrosis and cirrhosis, some authors advocate a longer-term antiviral drug therapy[67,86]. According to Bonacci M. et al., the use of corticosteroids in the CryoVas is associated with higher immunological response rates after virus elimination as a result of the DAAs therapy, which is also reasonable to take into account when discussing this problem[57]. At the same time, in patients with a persistent clinical and immunological activity of cryovasculitis after achieving the SVR, attempts are made to use low/moderate doses of corticosteroids and cyclophosphamide[22,40,51]. According to many authors, the CD20 monoclonal antibodies therapy aimed at suppressing B-cell clonal expansion can be effective both in the prevention and treatment of the MC relapses, including their clinical manifestations, such as the CryoVas and the NHL[61,87].

Therefore, in view of an absence of clear understanding of the likelihood and consequences of a persistent cryoglobulinemia, abnormal RF and C4 levels after a successful AVT, as well as the short time period since the introduction of the DAA-based regimens into clinical practice, longer and larger-scale studies are required to evaluate the results obtained. A special focus should be put on patients with persistent immunological disorders, which will further help to assess both the frequency and timing of their regression, as well as possible negative sequelae. The evidence obtained may help identify the predictors of such outcomes, and develop the approaches to modify treatment modalities.

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