

Cryoglobulinaemic vasculitis: new aspects

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The past decade saw substantial advances in our understanding of the pathophysiology and treatment of cryoglobulinaemic vasculitis (CV). CV is a systemic immune complex-mediated vasculitis predominantly affecting small vessels and associated with the presence of serum cryoglobulins, *i.e.* cold-precipitable immunoglobulins. CV is triggered by chronic hepatitis C virus (HCV) infection in the majority of cases, but it may occasionally also complicate the course of other chronic infections, connective tissue diseases and lymphoproliferative disorders. “Essential” or “idiopathic” CV is diagnosed in patients in whom no causative infectious agent or underlying disease can be identified (1, 2).

The common pathophysiologic denominator of the above mentioned disorders is clonal B-cell proliferation with cryoglobulin production. Mixed cryoglobulinaemia containing a monoclonal immunoglobulin (IgM) rheumatoid factor (RF) directed against the Fc segment of IgG and a polyclonal IgG component is usually detected in HCV-associated CV. When exposed to cold, the IgM-RF is apparently subject to conformational changes resulting in cryoprecipitation. Chronic antigenic challenge and receptor-mediated entry and infection of B-cells have been implicated in driving lymphoproliferation including the formation of ectopic lymphoid tissue in the liver and clonal B-cell expansion. HCV glycoproteins interact with receptors on the surface of B-cells, *e.g.* the HCV-E2 envelope protein with CD81 which associates with CD19 and CD21 to form the B-cell co-receptor complex. As a consequence the threshold for B-cell activation is lowered. B-cell receptors of clonally expanded B-cells cross-react with the HCV-NS3 non-structural protein and the Fc segment of IgG resulting in auto-IgG specificity. Circulating clonally expanded B-cells display a marginal-zone-like memory

B-cell phenotype and produce IgM-RF. Transition from benign lymphoproliferative disease into malignant non-Hodgkin lymphoma may be encountered in HCV-associated CV (1-3).

CV is secondary to the deposition of circulating cryoglobulins in the vessels causing vascular inflammation and damage. Although mixed cryoglobulinaemia can be found in up to 60% of HCV-infected patients, CV develops in less than 5%. Thus, the development of CV must be determined by a number of factors. Cryoglobulins are preferentially deposited in tissues with high blood flow per unit mass of tissues, *e.g.* skin, synovium, choroid plexus and glomerulus. Haemorheological and local factors such as blood viscosity and temperature play an additional role in the deposition of cryoglobulins and subsequent immune complex-mediated induction of inflammation. Cutaneous lesions represent the most frequent manifestations ($\geq 95\%$) in CV. Meltzer's triad (purpura, arthralgia, asthenia) is frequently found in CV as well as polyneuropathy (80%), renal involvement (40%), and Raynaud's phenomenon (35%) (1, 2). Earlier classification criteria were based on expert opinion, but lacked appropriate statistical support (4, 5). More recently, preliminary classification criteria for CV have been presented by a European multicentre task force by applying a methodology similar to the one employed for the classification criteria of Sjögren's syndrome. The proposed criteria showed a high specificity (93.6%) and good sensitivity (88.5%) for CV independent of the HCV-status (6). In this issue of *Clinical and Experimental Rheumatology*, Quartuccio *et al.* present their data on the performance of the CV-classification criteria by dissecting the two subsets, *i.e.* HCV-positive and HCV-negative CV, in a cohort of 500 patients presenting with cryoglobulinaemia.

Competing interests: none declared.

In addition, a subgroup-analysis was performed in patients with Sjögren's syndrome which represents the largest subgroup of HCV-negative CV-cases. Specificity and sensitivity of the criteria were high in HCV-positive (96.1% and 88.3%, respectively), HCV-negative CV (90.3% and 89.5%), and Sjögren's syndrome with CV (91.3% and 88.9%). The slightly lower specificity in HCV-negative CV was attributed to an overlap with related symptoms (e.g. arthralgia) found in HCV-negative controls with cryoglobulinaemia without vasculitis suffering from connective tissue diseases and other conditions. Interestingly, HCV-negative CV-cases showed a higher prevalence of some clinical items such as constitutional symptoms, arthralgia, and neurological manifestations. Thus, the recently developed classification criteria for CV can be equally and reliably applied both in HCV-positive and -negative CV (7). The study by Quartuccio *et al.* provides a confirmation of the good performance of the proposed CV-criteria. These data are relevant for the inclusion and analysis of HCV-positive and -negative CV-patients in future epidemiological and clinical studies (6, 7). Potential differences in the response to immunosuppressive treatment and adverse events between HCV-positive and -negative CV have been reported recently (8). Early studies showed that remission can be induced with interferon (IFN)- α plus ribavirin (RBV) in HCV-associated CV, but the response rate was lower than that observed in chronic hepatitis C treatment trials and neuropathy and glomerulonephritis remained resistant to IFN- α plus RBV treatment in the majority of CV-cases (9-11). Targeting both viral replication and clonal B-cell expansion with its sequelae by a combination therapy comprising B-cell depleting treatment with the monoclonal anti-CD20 antibody rituximab (RTX) administered once weekly for a month followed by antiviral treatment with the administration of pegylated (p)IFN- α plus RBV results in significantly higher remission-rates and a better outcome (12, 13). Based on these data the combination therapy with RTX and pIFN- α plus RBV has become the standard

treatment of HCV-associated CV with moderate to severe disease manifestations including glomerulonephritis and/or neuropathy in the meantime (10, 12, 13). By comparison, HCV-negative CV is rare and data on its course and treatment scarce. Some reports suggest that the response to RTX may be less favourable and adverse events more frequent in HCV-negative CV, whereas other studies showed similar responses to RTX in HCV-positive and -negative CV (8, 14). More recently, remission was induced with low-dose interleukin (IL)-2 in a phase 1/2a trial in 8 of 10 patients with HCV-associated CV suggestive of a potential novel non-cytotoxic "truly biologic" therapeutic approach. IL-2 treatment resulted in the expansion and activation of regulatory T-cells (Treg) associated with a decrease of memory B-cells and cryoglobulinaemia and an increase in complement levels. Of note, neuropathy proved to be resistant to IL-2 treatment in 2 patients. It was inferred that low-dose IL-2 tipped the Treg/effector T-cell (Teff) balance in favour of Treg while Teff were relatively spared from IL-2-mediated effects and inflammation and vasculitis flares not induced. The viral load did not increase in the IL-2 trial during treatment and follow-up until week 19 (15). However, longer follow-up and further studies are needed to address the question of sustained viral replication under IL-2 treatment and the outcome of viral elimination with pIFN- α plus RBV following IL-2 therapy. Of note, Treg have been shown to suppress the *in vitro* proliferation of virus-specific T-cells (16). Other future directions in the treatment of HCV-associated CV include the administration of antiviral triple therapy (pIFN- α , RBV and protease inhibitors telaprevir or boceprevir) subsequent to RTX induction and treatment stratification according to prognostic markers for the individual course and/or treatment response such as IFN λ 3 (*IL28B*)-gene polymorphisms (17, 18). Finally, new studies promise hope for an effective HCV-vaccine in a not too distant future (19).

In summary, the study by Quartuccio *et al.* (7) confirms the excellent perform-

ance of the recently proposed classification criteria in HCV-positive and -negative CV. Thus, the criteria provide a reliable basis for the inclusion of CV-patients in epidemiological and clinical studies. The study adds to a number of exciting studies and trials which have provided significant progress in our understanding of genetic, clinical and pathophysiological aspects of CV and cumulated in the advent of new treatment options during the last few years.

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