Clinical and Experimental Medicine
https://doi.org/10.1007/s10238-022-00808-1

REVIEW ARTICLE

The wide spectrum of cryoglobulinemic vasculitis and an overview of therapeutic advancements

Franco Dammacco[1] · **Gianfranco Lauletta**[1] · **Angelo Vacca**[1]

Received: 15 January 2022 / Accepted: 14 February 2022

Abstract

Immunoglobulins that reversibly precipitate at temperatures below 37 °C are called cryoglobulins (CGs). Cryoglobulinemia often manifests as cryoglobulinemic vasculitis (CV), whose symptoms range in severity from purpuric eruptions to life-threatening features. The majority of CV patients are infected with hepatitis C virus (HCV), whereas lymphoproliferative disorders or connective tissue diseases (CTD) are commonly diagnosed among patients with CV of non-infectious origin. In the absence of detectable associated disease, cryoglobulinemia is classified as "essential" (EMC). All HCV-positive CV patients should be given direct-acting antiviral agents (DAAs) that are consistently able to induce a sustained virologic response (SVR). Glucocorticoids (GCs) can mitigate CV-associated vasculitis, but they have no role as maintenance therapy. Cyclophosphamide restrains the hyperactive phase(s) of the disease and the post-apheresis rebound of newly synthesized CGs. Its use has been largely replaced by rituximab (RTX) in patients unresponsive to DAAs, patients progressing to B-cell non-Hodgkin lymphoma (B-NHL) and patients in whom CV persists or reappears after clearance of HCV. Therapeutic apheresis is an emergency treatment for CV patients with hyperviscosity syndrome. HCV-positive CV patients are at an increased risk of developing NHL, but the achievement of SVR can effectively prevent HCV-related NHL or induce the remission of an already established lymphoma, even without chemotherapy. The treatment of patients with IgM or IgG monoclonal cryoglobulins and an underlying immunoproliferative disorder is based on the regimens adopted for patients with the same B-cell malignancies but without circulating CGs. For patients with CTD, GCs plus alkylating agents or RTX are similarly effective as first-line therapy and in the relapse/refractory setting. In patients with EMC, treatment should consist of GCs plus RTX, with the dose of GCs tapered as soon as possible to reduce the risk of infectious complications.

Keywords Cryoglobulin · Cryoglobulinemic vasculitis · HCV · Non-Hodgkin lymphoma · Glucocorticoids · Rituximab · Therapeutic apheresis

Abbreviations

BAFF	B-lymphocyte activating factor
BMB	Belimumab
B-NHL	B-cell non-Hodgkin's lymphoma
BTK	Bruton tyrosine kinase
CG	Cryoglobulin
CI	Confidence interval
CPH	Cyclophosphamide
CV	Cryoglobulinemic vasculitis
DAAs	Direct-acting antiviral agents
DLBCL	Diffuse large B-cell lymphoma
eGFR	Estimated glomerular filtration rate
EMC	Essential mixed cryoglobulinemia
GCs	Glucocorticoids
GISC	Italian Group for the Study of Cryoglobulinemias
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HVS	Hyperviscosity syndrome
IFN	Interferon
MC	Mixed cryoglobulinemia

✉ Franco Dammacco
francesco.dammacco@uniba.it

Gianfranco Lauletta
gianfranco.lauletta@uniba.it

Angelo Vacca
angelo.vacca@uniba.it

[1] Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro" Medical School, Polyclinic, Piazza Giulio Cesare, 11, 70124 Bari, Italy

Published online: 28 March 2022

MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MPGN	Membranoproliferative glomerulonephritis
MZL	Marginal zone lymphoma
NAs	Nucleos(t)ide analogs
OR	Odds ratio
PDN	6-Methyl-prednisolone
pSS	Primary Sjögren syndrome
RBV	Ribavirin
RF	Rheumatoid factor
RTX	Rituximab
SLE	Systemic lupus erythematosus
SLVL	Splenic lymphoma with villous lymphocytes
SVR	Sustained virologic response
T1MoC	Type 1 monoclonal cryoglobulinemia
TA	Therapeutic apheresis
WM	Waldenström's macroglobulinemia

Introduction

The terms cryoglobulin (CG) and cryoglobulinemia were coined almost 75 years ago to indicate proteins that reversibly precipitate at temperatures below 37 °C and redissolve at body temperature [1]. According to their immunochemical structure, CGs can be classified into three main types: type I, consisting of a single monoclonal immunoglobulin, usually IgM or IgG; type II, formed by mixed monoclonal IgM/polyclonal IgG immune complexes; and type III, which are also mixed but the IgM and IgG are polyclonal [2]. In both type II and type III mixed cryoglobulinemia (MC), the IgM fraction has rheumatoid factor (RF) activity.

The amount of cryoprecipitate, called cryocrit, is expressed as a percentage of whole serum. Cryoglobulin-related illness, referred to as cryoglobulinemic vasculitis (CV), may manifest as a wide spectrum of symptoms that range in severity from purpuric eruptions to life-threatening conditions [3, 4]. Figure 1 summarizes the frequency of the clinical manifestations observed in our cohort of 440 hepatitis C virus (HCV)-positive patients with CV

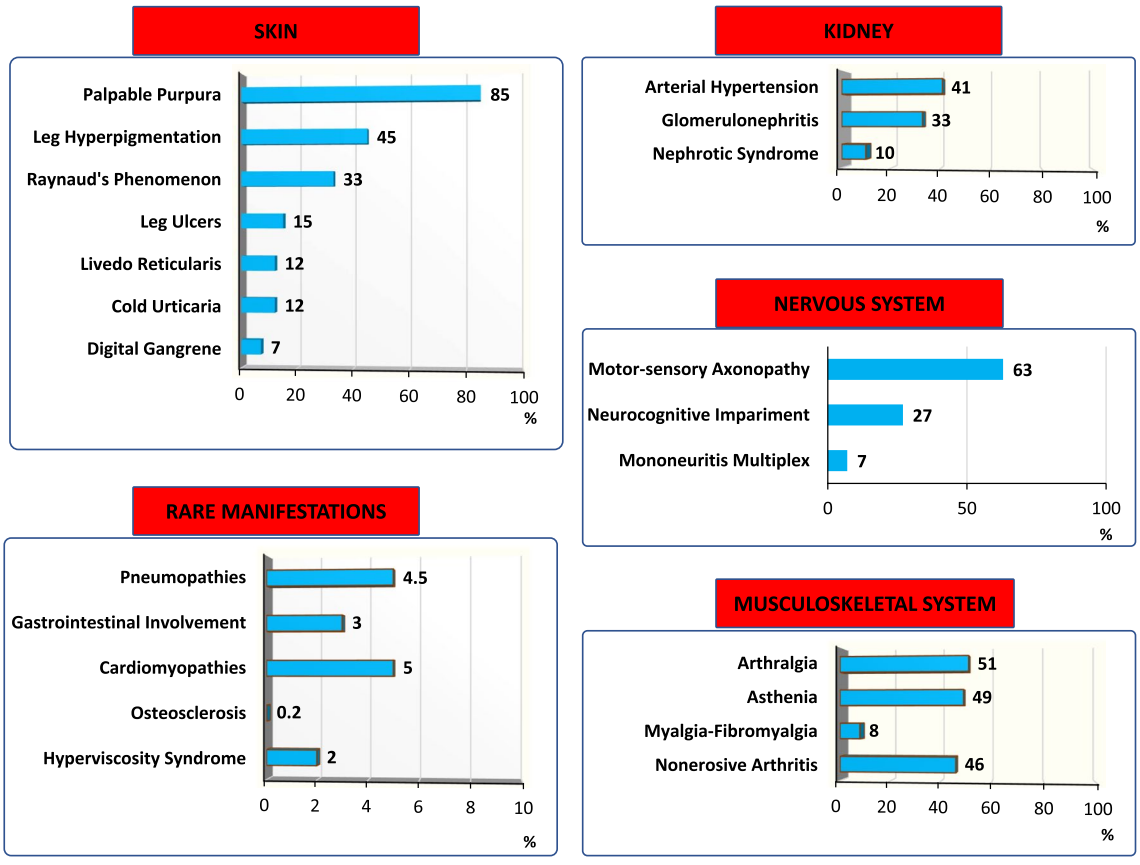

Fig. 1 The spectrum of clinical manifestations observed in the personal cohort of 440 patients with HCV-related cryoglobulinemic vasculitis (updated from the data reported in 2019 [5])

over a time span of 31 years: 39 (8.8%) had type I cryoglobulins, 284 (64.5%) type II, and 117 (26.6%) type III.

An underlying B-cell lymphoproliferative disorder, including Waldenström's macroglobulinemia (WM), multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS), and B-cell non-Hodgkin's lymphoma (B-NHL), is invariably diagnosed in patients with type I cryoglobulinemia [5, 6]. For many years, type II and type III MC, clinically characterized by the almost invariable presence of the triad purpura, arthralgia, and weakness syndrome, were classified as "essential," reflecting a lack of knowledge about their etiology [7]. At the beginning of the 1990s, unequivocal markers of HCV infection were detected in up to 90% of cryoglobulinemic patients, with no viral genotypic prevalence [8–10]. Conversely, CGs could be detected in 25–30% of HCV-positive patients [3, 4].

In a small number of patients, MC is associated with infectious agents other than HCV, such as hepatitis B virus (HBV) [11–13], hepatitis E virus [14], human immunodeficiency virus (HIV) [15], cytomegalovirus, Epstein Barr virus, parvovirus B19, pyogenic bacteria, leprosy, and candidiasis [11]. Figure 2 shows five groups of patients whose CV differs in its etiology and the percentage contributed by our cohort.

In this article, we review the therapeutic state of the art for all CV conditions and submit therapeutic statements that are based on a careful search of the literature, published guidelines, expert opinions, best available data, and our own experience. We also considered the recommendations of the European Association for the Study of the Liver (EASL), the American Association of the Study of Liver Disease, the Italian Group for the Study of Cryoglobulinemias (GISC), and the International Study Group of Extra-hepatic Manifestations Related to HCV Infection.

Therapeutic management of HCV-positive CV

The treatment of patients with HCV-positive CV should be established on an individual basis, depending on the degree of disease activity and the severity of the clinical symptoms. In patients with mild to moderate manifestations, an anti-HCV direct-acting antiviral (DAA) regimen is often highly effective. However, in those with widespread vasculitis, including renal involvement and severe neuropathy, a variable combination of DAAs plus non-HCV-directed agents may be needed, either to target symptoms, such as with low-to-intermediate doses of glucocorticoids (GCs) and therapeutic plasma exchange, or to interfere at the pathogenetic level, such as with the B-cell-depleting monoclonal antibody rituximab (RTX). Broad-spectrum immunosuppressive agents, such as cyclophosphamide (CPH), should be considered in refractory/relapsing patients (Fig. 3).

The primary goal of therapy for all HCV-infected patients, including those with CV, is to achieve a sustained virologic response (SVR), defined as a serum HCV RNA level below the limit of detection (≤ 15 IU/mL) as determined on blood testing 12 weeks after the completion of antiviral therapy (SVR-12) [16]. SVR is equated with cure and is usually accompanied by an improvement in liver function, including the normalization of transaminase and the regression or reduction of liver fibrosis [17, 18]. Viral eradication decreases the risk of hepatocellular carcinoma (HCC)

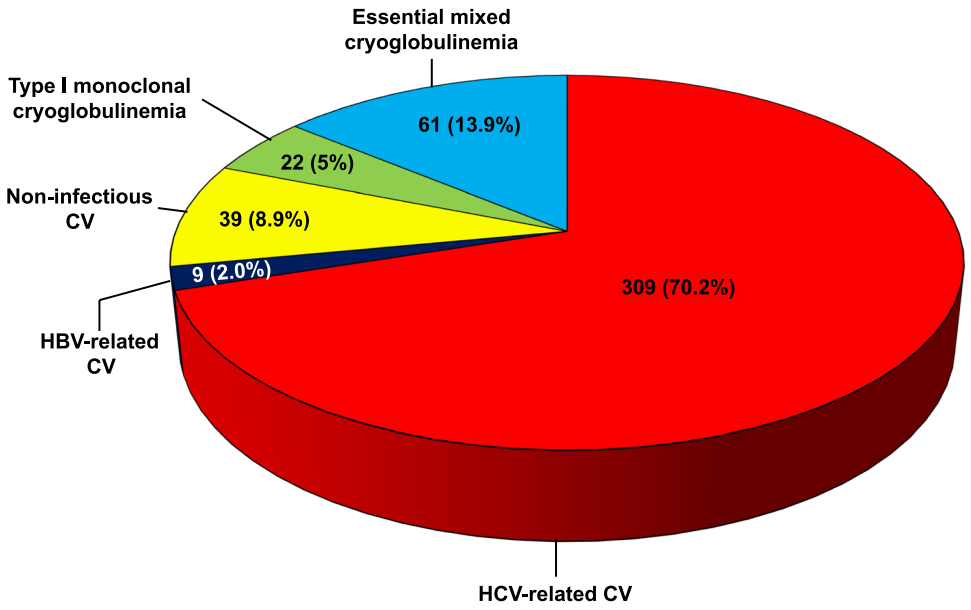

Fig. 2 Cryoglobulinemia can be detected in a wide range of clinical conditions, gathered in 5 diagnostic groups. The number of patients and the corresponding percentage of each group refers to our cohort of 440 patients, collected in a time frame of 31 years. *CV* cryoglobulinemic vasculitis

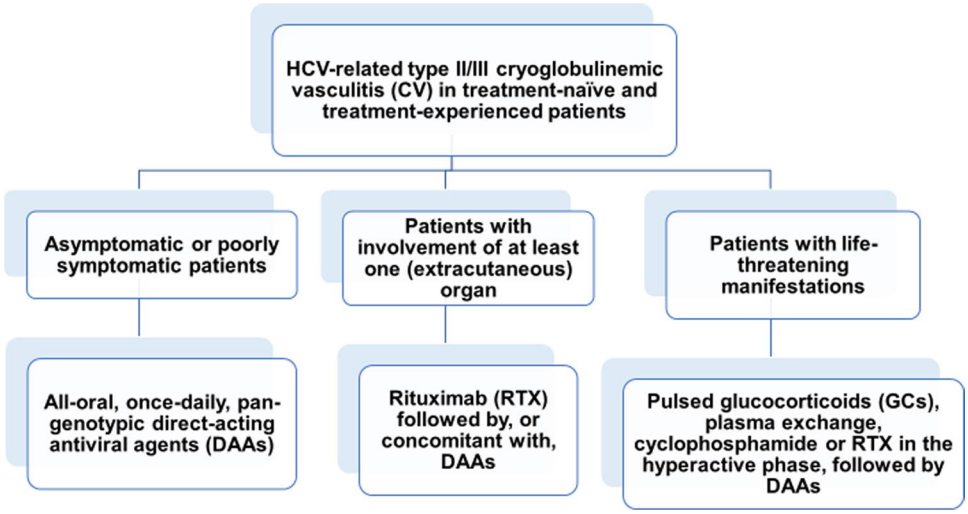

Fig. 3 Suggested treatment algorithm in patients with HCV-positive CV according to the severity of the clinical features. In the large majority of the studies, this treatment resulted in sustained virologic response in over 90% of the patients and disappearance of CV manifestations in percentages ranging from 30 to 87% (see Table 1)

by 85%, the risk of mortality from any cause by 74%, and liver-related mortality and the need for liver transplantation by 93% [19, 20].

Highly effective and well-tolerated DAAs are now the gold standard of care of HCV-positive patients, with or without CV. All-oral, once-daily, 8- to 12-week treatment regimens that include DAAs result in SVR in > 95% of patients across different HCV-positive populations [21, 22]. Following the demonstration of strikingly high rates of SVR achieved with first-generation NS3/4A protease inhibitors as well as NS5B polymerase and protease inhibitors in patients chronically infected with HCV, the same drugs were extended to the treatment of HCV-positive MC patients. Similar SVR rates were in fact obtained in a number of studies involving patients with HCV-associated CV [23–37] (Table 1).

The spectrum of interferon (IFN)-free, all-oral, once-daily DAAs highly effective across all viral genotypes and fibrosis stages has remarkably expanded in the last few years, resulting in SVR rates close to 100% in HCV-infected patients receiving first-line treatment regimens as well as in those with previous treatment failure [38, 39]. While CGs and their complications usually appear after a long-lasting HCV infection [40], the prompt administration of DAAs to patients with a newly diagnosed infection may avoid this outcome and thus, the development of HCV-related CV.

Statement All treatment-naïve and treatment-experienced HCV-positive patients with cryoglobulinemia should be promptly treated with pan-genotypic DAA regimens highly effective in the achievement of SVR and with a very good safety profile. DAAs can prevent or reduce HCV-related hepatic and extra-hepatic complications. Given their pan-genotypic effects, sofosbuvir/velpatasvir or glecaprevir/pibrentasvir treatment regimens can be employed in CV patients with HCV of unknown genotype and subtype. In this group, the SVR-12 rate is close to 100%. However, HCV genotyping and subtyping should still be performed, whenever available and affordable, in order to identify those HCV subtypes known to be poorly susceptible or resistant to NS5A inhibitors, as these patients will require tailored treatment.

The questionable role of GCs

Based on their ability to inhibit pro-inflammatory cytokines, GCs are commonly given in low-to-moderate doses for short periods (weeks to a few months) to patients with active CV, with the aim of mitigating vasculitis flares and alleviating arthralgias. However, the long-term administration of GCs, even at low doses, is not recommended, given their doubtful clinical utility and the inevitable onset of side effects [41, 42]. Nonetheless, in patients with an exacerbation of renal disease and in those with cutaneous and visceral life-threatening CV, pulsed intravenous high-dose GCs, with or without plasma exchange, should be considered as first-line treatment [43].

Statement The administration of GCs to CV patients should be restricted to those with the following conditions: (a) new-onset CV, to subdue vasculitis and arthralgias: 6-methyl-prednisolone (PDN) 0.1–0.5 mg/kg body weight/day, steadily tapered until discontinuation; (b) severe, multi-organ, life-threatening CV: PDN pulses of 0.5–1 g for 3 consecutive days followed by oral PDN 0.5 mg/kg/day, gradually tapered to 0.1–0.2 mg/kg/day until withdrawal after 1–2 months. Patients in either group can be administered GCs prior to, or concomitant with, DAAs. GCs have no role as maintenance therapy.

Table 1 Summary of the major studies on the treatment of HCV-related cryoglobulinemic vasculitis with all-oral direct-acting antiviral agents (DAAs)

Reference number	No. of patients (F/M)	No. of patients with P/W/A	No. of patients with kidney involvement	No. of patients with PNS involvement	Mean RF level (IU/mL)	Mean C4 level (g/L)	Antiviral regimen	SVR (%)	Disappearance of CV (%)
		Start → End	Start → End	Start → End	Start → E nd	Start → End			
[23]	24 (13/11)	16/0/14 → 0/0/0	5 → 1	16 → 1	26 → NR	0.10 → 0.17	SOF/RBV	74	46.1
[24]	12 (5/7)	6/0/7 → 1/0/4	7 → 4	4 → 2	9/10 pts → NR	0.11 → 0.16	SOF/RBV; SOF/SIM	83	44.4
[25]	44 (28/16)	32/34/26 → 2/5/8	4 → 0	28 → 4	131 → 39	12/24 < 0.1 → NR	SOF/RBV; SOF/DCV; SOF/SIM; SOF/LDV	100	39.5
[26]	35 (26/9)	23/25/11 → 2/1/1	7 → 2	18 → 5	80 → 20	0.02 → 0.12	3D-combo; SOF/LDV; SOF/SIM; SOF/DCV; ELB/GRZ; FAL/DBV; SIM/DCV; pIFN/DAAs	94	45
[27]	22 (14/8)	22/22/22 → 6/6/6	4 → 1	2 → 2	69.3 → 40.1	0.001 → 0.01	SOF/RIBA; 3D-combo ± RBV; SOF/SIM; SOF/DCV; SOF/LDV	100	54.5
[28]	18 (11/7)	15/NR/3 → 8/NR/0	10 → 7	5 → 4	NR → NR	NR → NR	pIFN/RBV/TR; pIFN/RBV/BR; pIFN/SOF/RBV; SOF/RBV; SOF/SIM; SOF/LDV ± RBV; 3D-Combo ± RBV	88.9	29.4
[29]	17 (NR)	82/NR/NR → NR/NR/NR	29.4 → NR	52.9 → NR	NR → NR	NR → NR	SOF/RBV; SOF/LDV; SOF/DCV ± RBV SOF/SIM; 3D-combo	100	63.6
[30]	41 (22/19)	31/NR/26 → 0/NR/0	5 → 1	21 → 4	47 → NR	0.08 → 0.14	SOF/DCV	100	50
[31]	148 (73/58)[a]	85/NR/94 → 19/NR/20	25 → 9	86 → 22	NR/NR	NR/NR	SOF/RBV; SOF/DCV; SOF/LDV; SOF/SIM	97.2	53
[32]	85 (56/29)	58/52/41 → 5/13/17	9 → 6	37 → 13	221 → < 50	0.09 → > 1.2	3Dcombo ± RBV; SOF/DCV ± RBV; SOF/LDV ± RBV; SOF/SIM ± RBV; SOF/RBV	90.6	NR
[33]	46 (34/12)	29/28/16 → 0/0/0	9 → 3	19 → 3	50 → 15	0.04 → 0.14	3Dcombo ± RBV; SOF/SIM; SOF/DCV; SOF/VEL; SOF/RBV	100	78

Table 1 (continued)

Reference number	No. of patients (F/M)	No. of patients with P/W/A	No. of patients with kidney involvement	No. of patients with PNS involvement	Mean RF level (IU/mL)	Mean C4 level (g/L)	Antiviral regimen	SVR (%)	Disappearance of CV (%)
		Start → End	Start → End	Start → End	Start → E nd	Start → End			
[34]	22 (11/11)	12/NR/12 → 4/NR/3	0 → 0	10 → 3	111 → 74	0.07 → 0.09	SOF/SIM; SOF/LDV; 3Dcombo; (± RBV)	95	5
[35]	45 (30/15)	38/NR/21 → NR/NR/NR	NR → NR	34 → NR	NR → NR	NR → NR	SOF/LDV ± RBV; SOF/VEL; SOF/SIM; SOF/RBV; SOF/DCV; 3Dcombo	100	87
[36]	45,260 (1525/43,735)	NR/NR/NR → NR/NR/NR	NA → NA	NA → NA	NA → NA	NA → NA	SOF; SIM; SOF/LDV; DCV; 3D-combo; EBV/GRZ; (± RBV)	92.2	NA
[37]	67 (43/24)	33/NR/36 → 14/NR/14	NR → NR	28 → 10	218 → 75	0.065 → 0.088	ASV/DCV; SOF/RBV; SOF/SIM; SOF/LDV; 3Dcombo; (± RBV)	95	19

CV cryoglobulinemic vasculitis, *DAAs* direct-acting antiviral agents, *DBV* deleobuvir, *DCV* daclatasvir, *ELB* elbasvir, *FAL* faldaprevir, *GRZ* grazoprevir, *LDV* ledipasvir, *NA* not applicable, *NR* not reported, *pIFN* pegylated interferon, *P/W/A* purpura/weakness/arthralgia, *RBV* ribavirin, S*OF* sofosbuvir, *SIM* simeprevir, *3D-combo* ombitasvir, paritaprevir, ritonavir, dasabuvir

[a]Although the sex distribution is incorrect, it has been reproduced as reported in the corresponding reference

CPH and other immunosuppressive agents

The immunological hallmark of HCV-related CV is a B-cell clonal expansion that occurs primarily in the liver, preferentially involves RF-synthesizing B-cells, and correlates with a high intrahepatic viral load. HCV plays a major role in the emergence and maintenance of B-cell clonalities [44]. Consequently, while abatement of the viral load can be achieved with DAAs, the deletion of B-cell clonalities will require the use of immunosuppressive agents.

Based on the experience acquired in patients with anti-neutrophil-cytoplasmic-antibody-associated vasculitis, intravenous boluses of the alkylating agent CPH are preferred to daily oral administration [45]. However, clinical trials comparing oral versus intravenous CPH in CV patients have not been performed, nor are data available on the potential use of other immunosuppressive agents, including methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine.

Statement Although CPH has been largely replaced by B-cell-depleting monoclonal antibodies, it can still be employed: (a) in patients with highly active, rapidly progressing, multi-organ CV, until the initial hyperactive phase has been overcome; (b) in combination with TA, in CV patients with clinical manifestations ascribable to high cryocrit levels, to prevent or reduce a post-apheresis rebound in CG synthesis.

B-cell-depleting monoclonal antibodies

The chimeric IgG1k monoclonal antibody RTX, directed against CD20 expressed on pre-B-cells and mature lymphocytes, deletes the CD20-positive B-cell clonalities expanded and activated in CV patients [44]. Randomized controlled trials, uncontrolled clinical studies, and retrospective analyses have demonstrated that RTX administration is followed by a remarkable improvement of the clinical features of CV in 65–80% of the patients [46–49]. The corresponding amelioration of laboratory parameters included a marked decrease in serum cryoglobulins, RF and anti-HCV titers, normalization of C4 levels, and depletion of the oligo-monoclonal expansion of the B-cell clones in peripheral blood and bone marrow [4, 47–49].

The "4 plus 2" RTX schedule (375 mg/m^2 of body-surface area, administered intravenously once a week for 4 consecutive weeks, followed by two additional doses 1 and 2 months later) was borrowed from the oncological setting [47, 48], but the similar efficacy of lower doses (250 mg/m^2 for 2 consecutive weeks) has also been demonstrated [50]. Low-dose RTX is a cost-effective and safe alternative for the treatment of refractory HCV-associated CV. However, a high-dose protocol consisting of 1000 mg of RTX on days 1 and 15 with a repeat, if required, of 1000–2000 mg every 6 months ("rheumatoid arthritis protocol") has also been employed [51, 52].

RTX-induced severe systemic reactions occurred in 6 of 22 (27.3%) CV patients [51]. The clinical presentation consisted of a life-threatening vasculitis flare or, less frequently, serum sickness syndrome, that have been ascribed to the formation of immune complexes between RTX and the IgM component (endowed with RF activity) of mixed CGs [51]. Another potential risk of RTX therapy in CV patients is the possibility of enhancing HCV viremia, thus worsening the chronic hepatitis. Inconsistent results have been reported, with an increased, though usually transient, viremia described by some authors [47, 53, 54], and no significant changes in viral titers by others [49, 55, 56]. The administration of DAAs combined with RTX should prevent or largely reduce this risk, but in the absence of suitably powered and properly controlled clinical trials whether these drugs should be given concomitantly or sequentially has not been clearly established [42, 57].

The two RTX biosimilars CT-P10 and GP2013 were shown to be equivalent to the originator product in terms of efficacy, pharmacokinetic, pharmacodynamic, safety, and tolerability in patients with B-NHL [58]. In a recent Italian polycenter study, CT-P10 was given to a cohort of 51 CV patients and the results were compared with a retrospective group of 75 consecutive patients treated with RTX originator. No significant differences were found between the two groups in terms of effectiveness and immune-mediated adverse events, independently of whether the patients treated with CT-P10 were RTX-naïve or switched from RTX, but the cost/efficacy ratio was higher in those receiving the RTX biosimilar [59].

Of particular interest, but still in an initial phase of clinical investigation, is the combined administration of the anti-B-cell activating factor monoclonal antibody belimumab (BMB) and RTX. The rationale of this strategy stems from the B-cell proliferation and differentiation supported by B-lymphocyte activating factor (BAFF or BLys, a member of tumor necrosis factor superfamily) that in turn results in increased immunoglobulin synthesis. BAFF is upregulated in several autoimmune diseases and, among HCV-positive patients, its levels are higher in those with than without MC [60]. Thus, the simultaneous and direct targeting of the BAFF axis and of B-cells may offer an effective new treatment for patients with CV. In a pilot study, four patients (one with pSS, one with HCV chronic hepatitis, and two with EMC), all of them with CV refractory to or relapsed after RTX, were treated with a combination of BMB plus RTX. Complete regression of the cutaneous and articular manifestations was achieved in three patients; polyneuropathy stabilized in two patients and improved in one [61]. Similar results were obtained in patients sequentially treated with RTX and BMB for

type II MC associated with pSS refractory to RTX alone [62, 63].

Statement The efficacy, safety, and acceptable side effects of RTX have been unequivocally demonstrated for the following conditions: (a) HCV-related CV unresponsive to or that relapsed after DAA administration; (b) as initial therapy in patients with severe or life-threatening CV, given alone or together with GCs, CPH, or TA depending on the clinical assessment, followed by etiologic treatment with DAAs once the critical clinical features have been controlled; (c) patients in whom CV progresses to B-NHL unresponsive to DAAs and requiring the administration of RTX alone or in association with a chemotherapy regimen; (d) patients in whom DAA administration resulted in viral clearance but CV persists or reappears and the circulating and bone marrow B-cell clonalities are not replaced by polyclonal populations. Neither the most suitable dosage schedule nor the pros and cons of the concomitant vs. sequential administration of RTX and DAAs has yet to be clearly defined.

Therapeutic apheresis (TA)

With the introduction of DAAs and the B-cell-depleting monoclonal antibody RTX, the American Society for Apheresis has modified its recommendations for patients with symptomatic/severe cryoglobulinemia. Thus, TA is now rated as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment [64].

With the exception of the rare cases in which an extremely high cryocrit results in a hyperviscosity syndrome (HVS) requiring emergency TA, the decision whether and when to start or terminate this procedure should not be based on the cryocrit level, because it is not a marker of disease activity. In patients with multi-organ CV and clinical manifestations such as MPGN, peripheral neuropathy, and inveterate non-healing skin ulcers, TA is able to induce clinical improvement in 70–80% of the patients [64]. TA can be administered alone or combined with GCs and B-cell-depleting agents, but it is more often used in conjunction with CPH to prevent or reduce a post-apheresis rebound of CG production [64, 65].

A comprehensive overview of the indications, effectiveness, and tolerance of TA was provided by a retrospective multi-center study of 159 CV patients, with HCV-related disease determined in 71% [66]. When the overall response was assessed after the last TA session or when the patient was last seen, it was rated very good (remission of all of CV-related conditions) in 12%, good (significant improvement) in 38%; partial/transient in 25%, and insufficient//unevaluable in 23%. However, the response assessment should be considered with caution, given the lack of a control group. Multi-organ life-threatening CV and impaired renal function were the variables independently associated with a poor or no response to TA. No remarkable adverse events were recorded in any of the patients included in this multi-center cohort study [66].

Statement TA is a second-line procedure for CV patients and has a good safety profile. It is the only treatment capable of rapidly reducing the burden of circulating CGs and viral particles. Although antiviral drugs and B-cell-depleting agents have reduced its use, TA should be considered for the following indications: (a) HVS, caused by high cryocrit values and the physico-chemical characteristics of the cryoprecipitating immune complexes; (b) multi-organ, life-threatening CV; (c) rapidly progressive renal failure that would otherwise result in irreversible kidney damage; (d) severe cryoglobulinemic neuropathy refractory to other treatments; (e) inveterate, unhealing skin ulcers, usually on the lower limbs.

TA is often combined with the administration of GCs and CPH to prevent or reduce a post-apheresis rebound of CG production, but an increased risk of infection should be taken into account for these combinations.

Chronic HCV infection, MC, and B-NHL

In addition to being hepatotropic, HCV is a lymphotropic virus [67]. HCV-infected B-lymphocytes can escape virus-specific T-cell responses, are clonally expanded, and are activated to secrete IgM molecules with RF activity. These features may result in an indolent stage of lymphoproliferation, as occurs in MC, or in frank B-NHL [67]. HCV has been linked to lymphomagenesis in patients with and without MC. A long latency, likely exceeding 15 years, occurs between HCV infection and the onset of NHL [3, 4]. Direct cellular transformation related to the presence of the virus and chronic antigenic stimulation are the two major, non-exclusive molecular mechanisms thought to underlie HCV-related lymphomagenesis. This topic is extensively described elsewhere [5, 68–70].

In Italy, the overall risk of B-NHL development in patients with chronic HCV infection is estimated to be 35-fold higher (or 12-fold higher, when non-aggressive lymphomas are excluded) than in the general population. Over 90% of the patients developing B-NHLs had type II MC [68]. In another Italian study, 15 years after the initial diagnosis of HCV infection the prevalence of NHL was 15% and 7% in patients with and without CV, respectively. By contrast, HCC occurred in a significantly lower percentage in patients with (11%) than without (20%) CV [71].

In a large international pooled analysis, 4784 adult cases of NHL were collected by 17 study centers from the Lymphoma Epidemiology Consortium, located in Europe, North

America, and Australia. The control group consisted of 6269 adults matched by age, sex, and study center. HCV infection was detected in 3.60% of the NHL patients and in 2.70% of the controls (odds ratio [OR]: 1.78; 95% confidence interval [CI]: 1.40–2.25). Subtype-specific characterization showed that HCV prevalence was associated with marginal zone lymphoma (MZL) (OR: 2.47; 95% CI 1.44–4.23), diffuse large B-cell lymphoma (DLBCL) (OR: 2.24; 95% CI 1.68–2.99), and lymphoplasmacytic lymphoma (OR: 2.57; 95% CI 1.14–5.79) [69].

Further convincing evidence of a causal relationship between chronic HCV infection and the onset of NHL was the observation that HCV eradication by antiviral therapy with IFN-α-2b alone or combined with ribavirin (RBV) could result in regression of splenic lymphoma with villous lymphocytes (SLVL) [72]. Given the anti-proliferative properties of IFN-α, these findings should be interpreted with caution, but with the advent of highly effective and toxicity-free DAAs it has become possible to ascertain whether, even in the absence of IFN-α, SVR achievement is also associated with NHL regression. The results obtained in relatively large cohorts of HCV-positive patients with NHL consistently indicate that, as in IFN-α plus or minus RBV, treatment with DAAs is able to induce a regression of indolent B-NHL [70, 73, 74].

A recent study consisted of 100 HCV-positive patients with indolent NHL treated with an IFN-free regimen [75]. Whether and in how many of these patients HCV infection was associated with CV was not specified. The SVR was 99% and the overall hematologic response 66% (23% complete responses and 43% partial responses), with the latter being significantly higher in MZL than in non-MZL patients. When treatment-naïve patients with indolent NHL were treated with DAAs alone and compared with a historical cohort of HCV-positive patients with indolent NHL treated with IFN-α, the SVR rate (close to 100%) was found to be higher in patients treated with DAAs, but those treated with IFN-α had a higher complete hematologic response rate and a higher median duration of response. It was therefore concluded that, based on its anti-proliferative activity, IFN-α has a greater anti-lymphoma effect than DAAs. Conversely, DAA treatment has a better tolerability profile and is safer than IFN-α therapy. The differences between the two groups in terms of overall survival and progression-free survival were not significant [75].

A point of interest is whether DAAs should be given before, concurrent with, or after immuno-chemotherapy. The decision should be taken on a case-by-case basis. In patients with a clinically indolent disease course, treatment should start with the administration of DAAs, based on the rationale of eradicating the viral trigger of lymphomagenesis, and in the expectation that viral clearance would result in tumor regression. However, in patients with advanced stage disease that has reached a point of no-return, cytoreductive immuno-chemotherapy may become a priority, with antiviral therapy postponed until the lymphoma has entered remission [76].

Statement HCV-infected patients, with or without MC, are at increased risk of developing NHL, with an OR ranging between 1.7 and 4.4 depending on genetic and/or environmental factors. SVR achieved with IFN-α-based therapy can effectively prevent HCV-related NHL, and a similar preventive effect has been observed in patients treated with DAAs.

In patients with HCV-related, indolent B-NHL who do not need an immediate cytoreductive treatment, HCV eradication should be prioritized, with DAAs as first-line treatment. The achievement of SVR may induce a remission of indolent lymphoma even without chemotherapy.

Given the clinical and histological heterogeneity of B-NHL, its optimal management must be differentiated. While antiviral treatment with DAAs may be sufficient for low-grade lymphomas, immuno-chemotherapy is usually required for patients with high-grade lymphomas. In patients with more advanced or more aggressive NHL requiring cytoreductive treatment, the decision to administer DAAs before, concomitant with, or after immuno-chemotherapy should be made on a case-by-case basis.

Therapeutic management of type 1 monoclonal cryoglobulinemia (T1MoC)

T1MoC has been detected in 10–22% of cryoglobulinemic patients and is characterized by the presence of a circulating monoclonal component of IgG isotype in 53–60% and of IgM isotype in ~ 40% [5, 6, 77]. All T1MoC patients (with rare exceptions) are HCV-negative, their cryocrit at diagnosis is usually higher than in those with type II or III MC, and an underlying B-cell lymphoproliferative disorder is almost always present as well. In the largest cohort of T1MoC patients assessed so far, consisting of 102 patients collected at the Mayo Clinic of Rochester (USA), a lymphoproliferative disorder was diagnosed in 94 patients (92%), including MGUS in 39 patients, MM in 20, and WM in 18 [6].

The clinical features of T1MoC include constitutional symptoms and a wide spectrum of signs and symptoms related to the vascular occlusions caused by the cryoprecipitates. Skin manifestations are found in 70–85% of the patients and include recurrent episodes of purpuric eruptions, *livedo reticularis*, acrocyanosis and Raynaud's syndrome, and in some cases necrotic unhealing ulcers usually localized to the lower limbs. Among the extra-cutaneous clinical features, peripheral polyneuropathy with sensory and, rarely, motor impairment is present in > 40% of the patients and mostly involves the lower extremities.

Proteinuria of variable degree, microhematuria, and increased blood urea nitrogen and creatinine levels are the typical signs of renal involvement, occurring in about 30% of the patients [5, 6, 77]. In some instances, patients with a high cryocrit develop a HVS, with symptoms consisting of blurry vision, recurrent epistaxis, dizziness, and somnolence [78]. Clinically silent HVS can be detected by tortuous blood vessels and venous sausaging, both seen on funduscopic examination [79].

Asymptomatic patients do not require treatment and can be managed by watchful waiting. In patients with T1MoC and a diagnosis of IgG or IgM MGUS, first-line treatment ranges from GCs alone to their combination with alkylating agents or nucleos(t)ide analogues (NAs). The addition of RTX has been shown to result in high response rates with acceptable toxicity [5, 77]. For patients with T1MoC and an underlying diagnosis of MM, treatment regimens include alkylating agents (such as melphalan, CPH or bendamustine), GCs, proteasome inhibitors (such as bortezomib and carfilzomib), immunomodulatory drugs (such as lenalidomide and pomalidomide), and monoclonal antibodies (such as daratumumab and elotuzumab). These approved agents can be combined in double or triple regimens, sometimes as high-dose therapy in conjunction with autologous stem cell transplantation rescue [80, 81]. Variable combinations of cytotoxic agents, with or without RTX and GCs, can be administered to patients whose T1MoC is associated with a B-NHL [5, 77].

Symptomatic T1MoC patients with WM, before starting therapy, should be tested for somatic mutations of the molecular markers MYD88^{L265P} and CXCR4, identified in 95–97% and up to 40%, respectively, of WM patients [82, 83]. By analogy with the treatment of non-cryoglobulinemic WM, a genomically driven therapeutic approach, such as depicted in Fig. 4, should be recommended, given that the patient's genomic profile can affect the clinical outcome [83]. Although several treatment options are presently available for WM patients, including alkylators, NAs, proteasome inhibitors, and monoclonal antibodies, the first-in-class oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib, as monotherapy, has been employed in patients with MYD88 and without CXCR4 mutations, both in frontline and relapse settings [84, 85]. For patients with MYD88 and CXCR4 mutations or without MYD88 or CXCR4 mutations, chemoimmunotherapy or proteasome-inhibitor-based regimens are preferred [86]. The ibrutinib plus RTX combination was shown to be highly effective, with a good safety profile, both in newly diagnosed patients and those with relapsed-refractory disease [87]. In addition, novel covalent and non-covalent second- and third-generation BTK inhibitors (such as acalabrutinib, zanubrutinib, and vecabrutinib) are emerging and are expected to further improve the therapeutic armamentarium for WM.

Patients with serum levels of the IgM monoclonal component > 4 g/dL should undergo TA before receiving RTX or receive a combination regimen based on chemotherapy in advance of RTX, to avoid or lessen the IgM flare, i.e., an initial upsurge in serum IgM levels that occurs in > 50% of patients treated with RTX [88].

Statement A watchful waiting approach is advisable for all asymptomatic T1MoC patients, whereas patients with signs and symptoms ascribable to the circulating monoclonal cryoglobulins can be treated with GCs alone or combined with RTX. In patients with high cryocrit and HVS, TA is able to rapidly remove sizable amounts of circulating cryoglobulins, resulting in prompt clinical improvement.

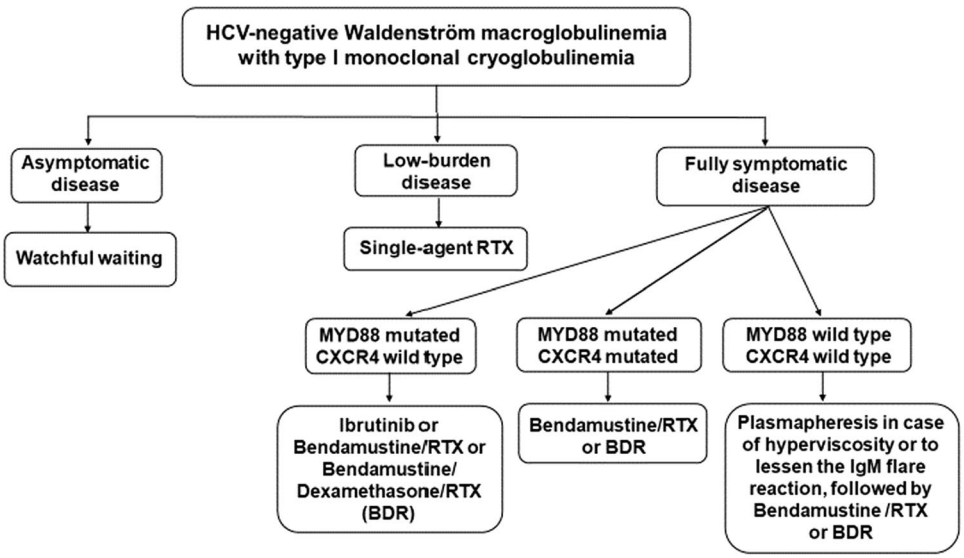

Fig. 4 Suggestion of a genomically driven therapeutic approach in patients with Waldenström macroglobulinemia and HCV-negative type I CV (Adapted from [84])

Therapeutic approaches to T1MoC patients with an underlying diagnosis of IgG or IgM MGUS, NHL, MM, or WM are largely based on the procedures adopted for patients with the same B-cell malignancies without cryoglobulinemia.

Treatment of CV patients with renal impairment

Renal involvement occurs in 30–50% of patients with HCV-associated cryoglobulinemia, the most common clinical form being membrano-proliferative glomerulonephritis (MPGN), which usually appears 3–5 years after the onset of purpura. Asymptomatic proteinuria (< 3 g/24 h), with or without microscopic hematuria, is found in 30–35% of patients, but proteinuria may reach the nephrotic range in roughly 20% of MPGN patients. Acute nephritic syndrome, macroscopic hematuria, acute or chronic renal failure, and oligoanuria each occur in 8–10% of patients [3, 89].

Although renal involvement often follows an indolent course and rarely reaches end-stage renal disease, the overall prognosis of patients with cryoglobulinemic MPGN is poor, given the frequent occurrence of arterial hypertension and cardiovascular complications, advanced liver disease, and difficult-to-treat infections [3, 90]. A renal biopsy is highly advisable as it can provide a reliable estimate of the extent of the kidney damage and will guide the therapeutic approach. Over 50% of the glomeruli are involved in diffuse MPGN, diagnosed in ~ 80% of patients, and < 50% in focal MPGN and mesangial proliferative glomerulonephritis, each diagnosed in ~ 10% of patients.

All CV patients with severe, possibly function-threatening or even life-threatening renal involvement should be treated with immunosuppressive agents, usually associated with GCs and TA. Etiologic therapy should be given when the clinical features have improved or stabilized. However, in patients with clinically indolent, self-limiting mesangial glomerulonephritis a DAA-based etiologic treatment remains the first-line therapeutic approach. In CV patients with glomerulonephritis, DAA therapy resulting in SVR-12 can induce an improvement of renal function, as shown by a reduction in proteinuria and serum creatinine levels, as well as an increase, albeit limited, in the estimated glomerular filtration rate (eGFR) [24]. An improvement in median eGFR and a reduction in median proteinuria following the administration of DAAs and the achievement of SVR-12 have been repeatedly reported [25, 26, 28, 30], although organ recovery usually lagged behind the achievement of SVR by 3–5 weeks [24].

The NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir exert strong antiviral activity across all six major HCV genotypes. Both agents are metabolized and cleared primarily through the biliary system, whereas their renal excretion is negligible, thus requiring no dose adjustment when administered to patients with renal failure [91]. In a multi-center, open-label, phase 3 trial that assessed the treatment efficacy and safety of glecaprevir in combination with pibrentasvir for 12 weeks in adults with HCV genotype 1–6 infection, compensated liver disease, and stage 4 or 5 chronic kidney disease (eGFR < 30 mL/min per 1.73 m^2), an SVR rate of 98% was achieved. Serious, mostly cardiovascular adverse events were reported in 24% of the patients [91].

Pharmacokinetic studies have shown that the renal excretion of grazoprevir, an HCV NS3/4A protease inhibitor, and elbasvir, an NS5A protein inhibitor, is detectable in < 1% of patients, thus excluding the need for a dose adjustment in those with chronic kidney disease. Based on this knowledge, in a study designed to assess an IFN-free, RBV-free, all-oral treatment regimen for patients with stage 4–5 chronic kidney disease and infected with HCV genotype 1, combined treatment with grazoprevir plus elbasvir yielded a 99% SVR-12, with a low rate of adverse events [92]. Thus, with new, well-tolerated DAA combinations that are not excreted through the kidneys, patients with all genotypes of HCV infection and chronic kidney diseases or end-stage renal disease are candidates for treatment.

Statement CV patients with clinical and/or laboratory signs of renal impairment should undergo, whenever possible, a renal biopsy to establish the extent of the renal damage and guide treatment planning. Based on the experience in HCV-positive patients with severe renal impairment but without CV, the preferred etiologic treatment is the fixed-dose combination of glecaprevir and pibrentasvir. A fixed dose of grazoprevir and elbasvir should be reserved for patients infected with HCV genotype 1b.

Non-HCV-related CV

Among patients with CV unrelated to HCV infection, three groups can be distinguished: (1) patients for whom an infectious agent other than HCV is presumed to be the underlying causative agent; (2) patients with autoimmune disorders, B-NHL, or occasional solid tumors; (3) patients with no identifiable associated disease responsible for CG production and thus diagnosed with essential mixed cryoglobulinemia (EMC).

Non-HCV-related infectious CV

In the French nationwide CryoVas survey [11], 18 patients had non-HCV-related infectious CV: eight with a viral infection, including HBV, cytomegalovirus, Epstein-Barr virus, parvovirus B19, and HIV. Pyogenic bacterial infections and isolated instances of parasitic and mycotic infections were also detected. Purpura was largely prevalent

(78%) among the clinical features at diagnosis, followed by glomerulonephritis, arthralgia/arthritis, peripheral neuropathy, cutaneous ulcers, and myalgia in decreasing proportions ranging from 28 to 11%. The GISC carried out a similar prospective observational study of 175 patients with HCV-unrelated (anti-HCV and HCV RNA negative) CV, including 15 (8.6%) who were HBsAg-positive in the absence of any coexistent disease [12].

The therapeutic approach in patients with HBV-related CV is the same as that in patients with chronic non-cryoglobulinemic HBV hepatitis [93]. In the absence of a true cure, these patients are usually treated with the long-term administration of an NA, such as entecavir, tenofovir, or adefovir, shown to reduce both mortality and the risk of liver cirrhosis and HCC, especially if a functional cure is achieved, i.e., the persistence of virological suppression while the patient is kept off therapy. However, infection reactivation following treatment cessation is a frequent event.

Entecavir and tenofovir are preferred over other NAs due to their established antiviral efficacy and lower rates of antiviral resistance [94, 95]. Monitoring at 6-month intervals is usually adopted, but in patients with renal impairment induced by CV the monitoring intervals should be shortened to every 3 months. The decision as to whether antiviral treatment can be safely discontinued should be made on an individual basis. In general, while patients without cirrhosis who achieve the desirable endpoint of HBsAg loss can safely stop treatment, those with cirrhosis should continue therapy. In patients with HBeAg seroconversion or a prolonged suppression of HBV DNA, NA therapy can be interrupted after a 12-month period of consolidation therapy whereas in patients with cirrhosis and HBeAg seroconversion or who test HBeAg-negative NAs should be continued indefinitely [93, 94].

The therapeutic management of patients with non-HCV- and non-HBV-related infectious CV is primarily based on the use of specific antimicrobial drugs, depending on the causative agent. No specific antimicrobial therapy is available for patients in whom cytomegalovirus, Epstein–Barr virus, or parvovirus B19 is the underlying infectious agent. Highly active anti-retroviral therapy, such as the combination lamivudine/tenofovir/efavirenz, should be given to CV patients mono-infected with HIV.

Statement A minority of patients with infectious CV are anti-HCV- and HCV-RNA-negative and are instead positive for other viruses or for pyogenic bacterial, parasitic and mycotic infections. These types of non-HCV-related infectious CV are rare, with the most common (3%) being chronic HBV infection.

The treatment of patients with HBV-related CV is usually the same as that of patients with non-cryoglobulinemic chronic HBV hepatitis, i.e., the long-term administration of a NA, usually entecavir or tenofovir.

Patients with non-HCV- and non-HBV-related infectious CV should receive an antimicrobial (antiviral, antibacterial, antiparasitic, or antifungal) agent that targets the causative organism. Low-to-medium doses of GCs are often added for short periods of time to address clinical manifestations such as purpura, arthralgias, and peripheral neuropathy.

CV with an identifiable but non-infectious associated disease

In a GISC prospective observational study of 175 patients with HCV-unrelated (anti-HCV- and HCV-RNA-negative) CV that excluded patients with HBV-associated liver disease or EMC, the spectrum of clinical diagnoses included primary Sjögren syndrome (pSS) in 21.1%, systemic lupus erythematosus (SLE) in 10.9%, other autoimmune disorders in 10.9%, lymphoproliferative diseases in 6.8%, and solid tumors (two cases of follicular thyroid carcinoma and one case each of lung and liver cancer) in 2.3% [12].

There are no standardized treatment procedures for patients with non-infectious CV. However, useful indications in terms of efficacy and safety can be extrapolated from the data obtained in a large cohort of 242 patients enrolled in a French multi-center CryoVas survey [96]. The 117 (48.3%) patients diagnosed with EMC are discussed below; in the remaining 125 patients, the causative factors were a connective tissue disease (mainly pSS and SLE) in 73 patients (30.1%) and a hematologic malignancy in 52 patients (21.5%). The administration of a combined regimen consisting of RTX plus GCs yielded higher rates of clinical, renal, and immunologic responses than achieved with GCs alone or alkylating agents plus GCs, whether as first-line therapy or in the relapsing/refractory setting. However, the greater efficacy of the RTX plus GCs combination was accompanied by the more frequent occurrence of severe infections, especially in older patients with renal impairment and in those receiving high-dose GCs [96].

In patients with pSS associated with CV, the phenotype of the pSS component is severe, with clinical features that often mask the more typical manifestations of pSS without CV. There is also a higher risk for the early development of NHL than in patients with HCV-related CV. In a multicenter study carried out on 71 patients with combined pSS and CV, treatment varied and included GCs (86%), hydroxychloroquine (80.3%), azathioprine (21.1%), methotrexate (22.5%), CPH (8.5%), RTX (18.3%), and TA (7%) [97].

Statement Combinations of GCs plus alkylating agents or GCs plus RTX achieve similar efficacy when used as first-line therapy in patients with non-infectious and non-essential

MC. Combined GCs plus RTX therapy is preferred in patients with relapsing/refractory disease as it is likely to achieve better clinical, renal, and immunologic responses. This combination results in a steroid-sparing effect, but the risk of infectious complications is higher. The GCs dose should therefore be tapered as soon as allowed by the clinical condition.

"Primary" or EMC

The condition characterized by the occurrence of cryoglobulins in the absence of any known disease responsible for their production is defined as EMC. An extensive microbiological screening for the presence of an underlying infectious agent and a search for an autoimmune disease or a lymphoproliferative disorder are therefore of utmost importance to rule out these causes. In the above-mentioned prospective, observational, multi-center study conducted by the GISC, EMC was diagnosed in 39.4% of the 175 patients with HCV-unrelated CV [12]. Among the 242 patients with non-infectious CV included in the French CryoVas survey, the percentage with EMC was even higher (48%) [96], whereas in a study from a single center that included 443 CV patients with all types of CV EMC was diagnosed in 11% [98]. Interestingly, compared to patients with secondary CV, the clinical course in those with EMC is more severe, with more frequent renal and peripheral nerve involvement [11]. In addition, such patients are likely to have a poor outcome and their risk of developing B-NHL is fourfold higher [99].

In the absence of an identifiable etiological agent, the treatment of EMC is largely symptomatic. Purpura, arthralgias/arthritis, and weakness are controlled by low-to-intermediate doses of GCs (0.3–0.5 mg of prednisone/kg/die) in the majority of patients, but higher doses (up to 1 mg of prednisone/kg/die) should be given when peripheral neuropathy and renal involvement are prominent clinical features. In more severe cases, GCs are combined with alkylating agents such as CPH to achieve a steroid-sparing effect; however, this combination results in clinical, renal, and immunologic responses in only 60–70% of patients. Higher response rates (80–85%) have been reported in patients with relapsing or refractory disease treated with a combined regimen consisting of GC, alkylating agents, and RTX, although at the expense of a higher rate of severe infections [43, 96].

Statement The clinical course of EMC is usually more severe than that of secondary CV in terms of more frequent renal and peripheral nerve involvement. Accordingly, these patients should be closely followed-up, given their increased risk of developing B-NHL.

Patients with severe EMC should be treated with a combination of GCs and RTX, with the latter added to curb the proliferation of cell clones responsible for CG production, in which case response rates may exceed 80%. However, because of the risk of infectious complications, especially in older patients and those with renal failure, the dose of GCs should be tapered as soon as warranted based on the clinical features.

The changing face of cryoglobulinemia

The introduction of DAAs in the therapy of chronic HCV infection has dramatically changed the outcome of CV, in that HCV eradication often prevents the development of cryoglobulinemia. As a consequence, HCV is expected to progressively lose its primacy as the most common cause of CV. In a French observational, longitudinal, cohort study carried out on 679 patients who met the inclusion criteria, a progressive decrease in the incidence of HCV-related MC was observed over time: while in 2011 62.5% of all MC cases were HCV-related, by 2018 the proportion had decreased to 33.3%, with the remaining 66.7% being mostly associated with a diagnosis of SLE (28.9%) or pSS (10.7%) [100]. The decline reflects the introduction of DAAs in the majority of European countries in 2014.

Thus, while previously up to 90% of MC cases were associated with HCV infection [4, 5], the causative landscape of MC and CV has remarkably changed. The widespread use of DAAs has resulted in a high rate of HCV eradication and a parallel progressive decrease in its extra-hepatic manifestations, including MC. As this decline in the occurrence of HCV-related MC can be expected to continue, in the near future autoimmune disorders will come to represent the leading cause of MC and CV [100].

Statement In parallel with the introduction of DAAs and their widespread use in the treatment of patients with chronic HCV infection, SVR rates are now close to 100%, such that the prevalence of HCV-related MC is steadily decreasing, a trend that will probably continue in the years to come. As a consequence, HCV should no longer be considered the major causative agent underlying the onset of MC and CV, as the most frequent conditions are now autoimmune diseases, especially pSS and SLE.

This changing landscape underscores the overarching importance of an etiologic determination in each MC patient in order to adopt the most suitable ("personalized") therapeutic approach.

Vaccines in patients with CV

Vaccination is a preventive rather than a therapeutic procedure and may therefore seem off topic in a paper dedicated to the therapy of CV. However, we feel it is appropriate to

briefly address the timing, efficacy, and duration of immunization in immunocompromised patients such as those with CV. In addition to their age (commonly older than 65), CV patients frequently have liver, renal, and neurological impairments, co-morbidities, including diabetes mellitus and cardiomyopathy, and a history of treatment with GCs, immunosuppressives, and biologic agents, all of which contribute to their immunological frailty.

Because immunocompromised patients are at high-risk for severe influenza and invasive pneumococcal diseases, they should be strongly advised to receive a quadrivalent influenza vaccine (two strains of influenza A and two of influenza B) and a pneumococcal conjugate 13-valent vaccine or a pneumococcal polysaccharide 23-valent vaccine [101, 102]. In addition, clinical experience has shown that CV patients are at risk of varicella zoster virus reactivation. As this baseline risk is enhanced by drugs such as CPH and RTX, especially when used in combination with GCs, before starting therapies capable of viral reactivation these patients should be vaccinated with a two-dose adjuvanted recombinant subunit anti-herpes zoster vaccine [103]. Moreover, given the continuing SARS-CoV-2 pandemic, it should also be noted that in CV patients infected with the virus the clinical course of COVID-19 is likely to be serious, including a higher risk of hospitalization and death. Thus, CV patients should be regularly vaccinated against SARS-CoV-2, preferably with an mRNA vaccine such as BNT162b2 or mRNA-1273 [104].

Although for all types of vaccines there is a risk of vaccine-induced autoimmunity, the risk-to-benefit ratio for CV patients strongly favors vaccination [102]. In addition to safety, the effectiveness and duration of immunization should be taken into consideration. There is convincing evidence that the immunologic responses to influenza and pneumococcal vaccines are impaired in patients treated with GCs and RTX [105, 106]. A similar high prevalence of impaired immunogenicity to COVID-19 vaccines, in terms of neutralizing IgG antibody levels, has been demonstrated in patients with systemic autoimmune diseases (including CV) treated with GCs, RTX, or mycophenolate mofetil [107].

Statement CV patients are immunologically frail and at high risk of infectious complications. They should therefore be strongly advised to be vaccinated, notably against influenza virus, pneumococci, varicella zoster virus, and SARS-CoV-2. In patients with severe and life-threatening CV, the vasculitis should be brought under control before any vaccine is administered.

Whenever possible, patients should be vaccinated before starting GCs or immunosuppressive/biologic agents. The potential risk of a CV flare triggered by vaccine-induced immune stimulation is largely outweighed by the advantages of protective immunity.

Patients already under treatment with RTX, and possibly with other immunosuppressive agents, should be vaccinated 6 months or longer after the last infusion or at least 4 weeks before the next course of RTX, to optimize the vaccine response [101]. However, when clinical or environmental circumstances require prompt prophylaxis, patients may be vaccinated irrespective of timing recommendations, though at the expense of reduced vaccine efficacy.

Conclusions and future directions

This review has examined the full clinical spectrum of CV and the corresponding therapeutic strategies. Patients with a mild clinical course who do not qualify for therapy should nonetheless undergo periodic monitoring, given the persisting risk of vasculitis flares. Whenever possible, a thorough examination, accurate screening for infectious agents, and an exact determination of any underlying or associated disease are treatment prerequisites. Only cryoglobulinemic patients in whom a causative factor cannot be determined despite extensive testing are classified as having "essential" MC.

The stunning success of DAAs in eradicating HCV in virtually all infected patients has altered the landscape of MC. Thus, the overall incidence of MC has steadily decreased and non-infectious CVs, including both those related to connective tissue diseases or hematologic disorders and EMC, are progressively replacing HCV as the major cause of this disease [100].

The long-term outcome of the minority of patients with HCV-related CV in whom, despite DAA-induced SVR, circulating CGs, purpuric eruptions, and other clinical manifestations persist or reappear at variable intervals remains to be ascertained. Circumstantial evidence indicates that these patients are at high risk of developing NHL [99], but biomarkers able to identify potentially modifiable risk factors that would prevent neoplastic progression or at least allow its early detection are still lacking. New drugs and therapeutic approaches for these patients at risk are also needed.

Patients with CV associated with systemic autoimmune diseases and those with EMC represent a therapeutic challenge. In the latter, the absence of a causative agent hinders etiologic treatment. Therapy consisting of GCs plus RTX (or CPH or mycophenolate mofetil) is not only GCs-sparing but in most patients yields better results than obtained with GCs alone in terms of clinical, renal, and immunologic responses. However, the overall therapeutic results are still not satisfactory, due to partial responses and relatively frequent relapses [96]. Whether the favorable clinical response observed in a pilot study of four patients with refractory CV treated with a combination of RTX plus BMB [61] will be confirmed in controlled studies with larger cohorts of patients remains to

be determined, as does whether this strategy is effective in the relapsed/refractory setting and as frontline therapy for non-infectious CV. Additional open questions include the long-term effects of this treatment on immune responses, the response duration, and possible re-treatment and maintenance strategies.

The treatment statements in this review were derived based on a careful search of the literature that included expert opinions, the recommendations and clinical practice guidelines of international and national scientific societies and study groups, and our own experience. Yet, suitably powered prospective studies are eagerly awaited to confirm, modify, or further validate these summary statements, to fill in key gaps in knowledge, and to resolve points of contention.

Additional issues that merit consideration are the initial selection of the compounds, the risks and benefits of their combination and switching, as well as possible dose adjustments, maintenance modalities, drug de-escalation, exit strategies, and the treatment of relapses. The resulting therapeutic decisions will need to incorporate disease phenotype, degree of activity, concomitant morbidities, individual effectiveness, and the possible occurrence of side effects.

Author contributions FD conceived and designed the study, had full access to all the data in the study, wrote the manuscript and take responsibility for the integrity of the data and the accuracy of the analysis. GL retrieved and collected the data. AV revised the manuscript for important intellectual content. All authors reviewed the manuscript, approved the draft submission, and accept responsibility for all aspects of this study.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declarations

Conflict of interests The authors have no relevant financial or non-financial interests to disclose.

References

1. Lerner AB, Watson CJ. Studies of cryoglobulins; unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin). Am J Med Sci. 1947;214(4):410–5.
2. Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. Am J Med. 1974;57(5):775–88.
3. Roccatello D, Saadoun D, Ramos-Casals M, et al. Cryoglobulinaemia. Nat Rev Dis Primers. 2018;4(1):11.
4. Dammacco F, Lauletta G, Russi S. Clinical practice: hepatitis C virus infection, cryoglobulinemia and cryoglobulinemic vasculitis. Clin Exp Med. 2019;19(1):1–21.
5. Terrier B, Karras A, Kahn JE, et al. The spectrum of type I cryoglobulinemia vasculitis: new insights based on 64 cases. Medicine (Baltimore). 2013;92(2):61–8.
6. Sidana S, Rajkumar SV, Dispenzieri A, et al. Clinical presentation and outcomes of patients with type 1 monoclonal cryoglobulinemia. Am J Hematol. 2017;92(7):668–73.
7. Meltzer M, Franklin EC. Cryoglobulinemia–a study of twenty-nine patients I IgG and IgM cryoglobulins and factors affecting cryoprecipitability. Am J Med. 1966;40(6):828–36.
8. Ferri C, Greco F, Longombardo G, et al. Antibodies against hepatitis C virus in mixed cryoglobulinemia patients. Infection. 1991;19(6):417–20.
9. Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med. 1992;327(21):1490–5.
10. Dammacco F, Sansonno D. Antibodies to hepatitis C virus in essential mixed cryoglobulinaemia. Clin Exp Immunol. 1992;87(3):352–6.
11. Terrier B, Marie I, Lacraz A, et al. Non HCV-related infectious cryoglobulinemia vasculitis: results from the French nationwide CryoVas survey and systematic review of the literature. J Autoimmun. 2015;65:74–81.
12. Galli M, Oreni L, Saccardo F, et al. HCV-unrelated cryoglobulinaemic vasculitis: the results of a prospective observational study by the Italian Group for the Study of Cryoglobulinaemias (GISC). Clin Exp Rheumatol. 2017;35 Suppl 103(1):67–76.
13. Mazzaro C, Dal Maso L, Urraro T, et al. Hepatitis B virus related cryoglobulinemic vasculitis: a multicentre open label study from the Gruppo Italiano di Studio delle Crioglobulinemie - GISC. Dig Liver Dis. 2016;48(7):780–4.
14. Bazerbachi F, Leise MD, Watt KD, Murad MH, Prokop LJ, Haffar S. Systematic review of mixed cryoglobulinemia associated with hepatitis E virus infection: association or causation? Gastroenterol Rep (Oxf). 2017;5(3):178–84.
15. Kosmas N, Kontos A, Panayiotakopoulos G, Dimitrakopoulos A, Kordossis T. Decreased prevalence of mixed cryoglobulinemia in the HAART era among HIV-positive, HCV-negative patients. J Med Virol. 2006;78(10):1257–61.
16. Chen J, Florian J, Carter W, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013;144(7):1450-1455.e2.
17. Carrat F, Fontaine H, Dorival C, French ANRS CO22 Hepather cohort, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting anti-viral treatment: a prospective cohort study. Lancet. 2019;393(10179):1453–64.
18. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584–93.
19. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting anti-viral agents. Hepatology. 2020;71(1):44–55.
20. Mahale P, Engels EA, Li R, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. Gut. 2018;67(3):553–61.
21. Feld JJ, Jacobson IM, Hézode C, ASTRAL-1 Investigators, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373(27):2599–607.
22. Foster GR, Afdhal N, Roberts SK, ASTRAL-2 Investigators; ASTRAL-3 Investigators, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. 2015;373(27):2608–17.
23. Saadoun D, Thibault V, Si Ahmed SN, et al. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia

vasculitis: VASCUVALDIC study. Ann Rheum Dis. 2016;75(10):1777–82.
24. Sise ME, Bloom AK, Wisocky J, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting anti-viral agents. Hepatology. 2016;63(2):408–17.
25. Gragnani L, Visentini M, Fognani E, et al. Prospective study of guideline-tailored therapy with direct-acting anti-virals for hepatitis C virus-associated mixed cryoglobulinemia. Hepatology. 2016;64(5):1473–82.
26. Bonacci M, Lens S, Londoño MC, et al. Virologic, clinical, and immune response outcomes of patients with hepatitis C virus-associated cryoglobulinemia treated with direct-acting antivirals. Clin Gastroenterol Hepatol. 2017;15(4):575-583.e1.
27. Lauletta G, Russi S, Pavone F, Vacca A, Dammacco F. Direct-acting anti-viral agents in the therapy of hepatitis C virus-related mixed cryoglobulinaemia: a single-centre experience. Arthritis Res Ther. 2017;19(1):74.
28. Emery JS, Kuczynski M, La D, et al. Efficacy and safety of direct acting anti-virals for the treatment of mixed cryoglobulinemia. Am J Gastroenterol. 2017;112(8):1298–308.
29. Sollima S, Milazzo L, Antinori S, Galli M. Direct-acting antivirals and mixed cryoglobulinemia vasculitis: long-term outcome of patients achieving HCV eradication. Am J Gastroenterol. 2017;112(11):1753–4.
30. Saadoun D, Pol S, Ferfar Y, et al. Efficacy and safety of sofosbuvir plus daclatasvir for treatment of HCV-associated cryoglobulinemia vasculitis. Gastroenterology. 2017;153(1):49-52.e5.
31. Cacoub P, Si Ahmed SN, Ferfar Y, et al. Long-term efficacy of interferon-free anti-viral treatment regimens in patients with hepatitis C virus-associated cryoglobulinemia vasculitis. Clin Gastroenterol Hepatol. 2019;17(3):518–26.
32. Gragnani L, Cerretelli G, Lorini S, et al. Interferon-free therapy in hepatitis C virus mixed cryoglobulinaemia: a prospective, controlled, clinical and quality of life analysis. Aliment Pharmacol Ther. 2018;48(4):440–50.
33. Bonacci M, Lens S, Mariño Z, et al. Long-term outcomes of patients with HCV-associated cryoglobulinemic vasculitis after virologic cure. Gastroenterology. 2018;155(2):311-315.e6.
34. Mazzaro C, Dal Maso L, Quartuccio L, et al. Long-term effects of the new direct anti-viral agents (DAAs) therapy for HCV-related mixed cryoglobulinaemia without renal involvement: a multicentre open-label study. Clin Exp Rheumatol. 2018;36 Suppl 111(2):107–14.
35. Visentini M, Del Padre M, Colantuono S, et al. Long-lasting persistence of large B-cell clones in hepatitis C virus-cured patients with complete response of mixed cryoglobulinaemia vasculitis. Liver Int. 2019;39(4):628–32.
36. El-Serag HB, Christie IC, Puenpatom A, Castillo D, Kanwal F, Kramer JR. The effects of sustained virological response to direct-acting anti-viral therapy on the risk of extrahepatic manifestations of hepatitis C infection. Aliment Pharmacol Ther. 2019;49(11):1442–7.
37. Pozzato G, Mazzaro C, Artemova M, et al. Direct-acting antiviral agents for hepatitis C virus-mixed cryoglobulinaemia: dissociated virological and haematological responses. Br J Haematol. 2020;191(5):775–83.
38. Vermehren J, Serfert Y, Cornberg M, et al. Sofosbuvir, velpatasvir, and voxilaprevir for patients with failure of previous direct-acting anti-viral therapy for chronic hepatitis C: results from the German Hepatitis C-Registry (DHC-R). Z Gastroenterol. 2020;58(9):841–6.
39. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series*. J Hepatol. 2020;73(5):1170–218.
40. Ferri C, Ramos-Casals M, Zignego AL, ISG-EHCV coauthors, et al. International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. Autoimmun Rev. 2016;15(12):1145–60.
41. Pietrogrande M, De Vita S, Zignego AL, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients. Autoimmun Rev. 2011;10(8):444–54.
42. Dammacco F, Sansonno D. Therapy for hepatitis C virus-related cryoglobulinemic vasculitis. N Engl J Med. 2013;369(11):1035–45.
43. Galli M, Monti G, Marson P, et al. Recommendations for managing the manifestations of severe and life-threatening mixed cryoglobulinemia syndrome. Autoimmun Rev. 2019;18(8):778–85.
44. Sansonno D, Dammacco F. Hepatitis C virus, cryoglobulinaemia, and vasculitis: immune complex relations. Lancet Infect Dis. 2005;5(4):227–36.
45. de Groot K, Harper L, Jayne DR, EUVAS (European Vasculitis Study Group), et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150(10):670–80.
46. Sansonno D, De Re V, Lauletta G, Tucci FA, Boiocchi M, Dammacco F. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. Blood. 2003;101(10):3818–26.
47. Dammacco F, Tucci FA, Lauletta G, et al. Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. Blood. 2010;116(3):343–53.
48. Ferri C, Cacoub P, Mazzaro C, et al. Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: results of multicenter cohort study and review of the literature. Autoimmun Rev. 2011;11(1):48–55.
49. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum. 2012;64(3):843–53.
50. Visentini M, Ludovisi S, Petrarca A, et al. A phase II, single-arm multicenter study of low-dose rituximab for refractory mixed cryoglobulinemia secondary to hepatitis C virus infection. Autoimmun Rev. 2011;10(11):714–9.
51. Sène D, Ghillani-Dalbin P, Amoura Z, Musset L, Cacoub P. Rituximab may form a complex with IgMkappa mixed cryoglobulin and induce severe systemic reactions in patients with hepatitis C virus-induced vasculitis. Arthritis Rheum. 2009;60(12):3848–55.
52. Buch MH, Smolen JS, Betteridge N, Rituximab Consensus Expert Committee, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(6):909–20.
53. Lake-Bakaar G, Dustin L, McKeating J, Newton K, Freeman V, Frost SD. Hepatitis C virus and alanine aminotransferase kinetics following B-lymphocyte depletion with rituximab: evidence for a significant role of humoral immunity in the control of viremia in chronic HCV liver disease. Blood. 2007;109(2):845–6.
54. Petrarca A, Rigacci L, Caini P, et al. Safety and efficacy of rituximab in patients with hepatitis C virus-related mixed cryoglobulinemia and severe liver disease. Blood. 2010;116(3):335–42.
55. Saadoun D, Resche Rigon M, Sene D, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood. 2010;116(3):326–34.
56. Sneller MC, Hu Z, Langford CA. A randomized controlled trial of rituximab following failure of anti-viral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis. Arthritis Rheum. 2012;64(3):835–42.
57. Ramos-Casals M, Zignego AL, Ferri C, International Study Group of Extrahepatic Manifestations related to HCV

(ISG-EHCV), et al. Evidence-based recommendations on the management of extrahepatic manifestations of chronic hepatitis C virus infection. J Hepatol. 2017;66(6):1282–99.
58. Brink M, Kahle XU, Vermaat JSP, et al. Impact of rituximab biosimilars on overall survival in diffuse large B-cell lymphoma: a Dutch population-based study. Blood Adv. 2021;5(15):2958–64.
59. Vacchi C, Visentini M, Gragnani L, et al. Safety and effectiveness of biosimilar of Rituximab CT-P10 in the treatment of cryoglobulinemic vasculitis: the MARBLe study (Mixed cryoglobulinemiA Rituximab BiosimiLar). Intern Emerg Med. 2021;16(1):149–56.
60. Landau DA, Rosenzwajg M, Saadoun D, Klatzmann D, Cacoub P. The B lymphocyte stimulator receptor-ligand system in hepatitis C virus-induced B cell clonal disorders. Ann Rheum Dis. 2009;68(3):337–44.
61. Saadoun D, Ghembaza A, Riviere S, et al. Rituximab plus belimumab in non-infectious refractory cryoglobulinemia vasculitis: a pilot study. J Autoimmun. 2021;116:102577.
62. Pouchelon C, Visentini M, Emmi G, et al. Management of non-viral mixed cryoglobulinemia vasculitis refractory to rituximab: data from a European collaborative study and review of the literature. Autoimmun Rev. 2022;21(4):103034.
63. Chevalier K, Belkhir R, Seror R, Mariette X, Nocturne G. Efficacity of a sequential treatment by anti-CD 20 monoclonal antibody and belimumab in type II cryoglobulinaemia associated with primary Sjögren syndrome refractory to rituximab alone. Ann Rheum Dis. 2020;79(9):1257–9.
64. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the seventh special issue guidelines on the use of therapeutic apheresis. J Clin Apher. 2016;31(3):149–62.
65. Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. Lancet. 2012;379(9813):348–60.
66. Marson P, Monti G, Montani F, et al. Apheresis treatment of cryoglobulinemic vasculitis: a multicentre cohort study of 159 patients. Transfus Apher Sci. 2018;57(5):639–45.
67. Hatano Y, Ideta T, Hirata A, et al. Virus-driven carcinogenesis. Cancers (Basel). 2021;13(11):2625.
68. Dammacco F, Gatti P, Sansonno D. Hepatitis C virus infection, mixed cryoglobulinemia, and non-Hodgkin's lymphoma: an emerging picture. Leuk Lymphoma. 1998;31(5–6):463–76.
69. de Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol. 2008;6(4):451–8.
70. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol. 2013;59(1):169–77.
71. Lauletta G, Russi S, Conteduca V, Sansonno L, Dammacco F, Sansonno D. Impact of cryoglobulinemic syndrome on the outcome of chronic hepatitis C virus infection: a 15-year prospective study. Medicine (Baltimore). 2013;92(5):245–56.
72. Hermine O, Lefrère F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med. 2002;347(2):89–94.
73. Arcaini L, Besson C, Frigeni M, et al. Interferon-free anti-viral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Blood. 2016;128(21):2527–32.
74. Masarone M, Persico M. Hepatitis C virus infection and non-hepatocellular malignancies in the DAA era: a systematic review and meta-analysis. Liver Int. 2019;39:1292–306.
75. Frigeni M, Besson C, Visco C, et al. Interferon-free compared to interferon-based anti-viral regimens as first-line therapy for B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Leukemia. 2020;34(5):1462–6.
76. Zignego AL, Ramos-Casals M, Ferri C, ISG-EHCV, et al. International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement. Autoimmun Rev. 2017;16(5):523–41.
77. Harel S, Mohr M, Jahn I, et al. Clinico-biological characteristics and treatment of type I monoclonal cryoglobulinaemia: a study of 64 cases. Br J Haematol. 2015;168(5):671–8.
78. Muchtar E, Magen H, Gertz MA. How I treat cryoglobulinemia. Blood. 2017;129(3):289–98.
79. Dammacco R, Lisch W, Kivelä TT, et al. the spectrum of ocular manifestations in patients with Waldenström's macroglobulinemia. Ocul Immunol Inflamm. 2021;16:1–10.
80. Terpos E, Mikhael J, Hajek R, et al. Management of patients with multiple myeloma beyond the clinical-trial setting: understanding the balance between efficacy, safety and tolerability, and quality of life. Blood Cancer J. 2021;11(2):40.
81. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol. 2021;22(3):e105–18.
82. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012;367(9):826–33.
83. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014;123(11):1637–46.
84. Treon SP, Xu L, Guerrera ML, et al. Genomic landscape of Waldenström macroglobulinemia and its impact on treatment strategies. J Clin Oncol. 2020;38(11):1198–208.
85. Castillo JJ, Meid K, Gustine JN, et al. Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia. Leukemia. 2022;36(2):532–9.
86. Sarosiek S, Treon SP, Castillo JJ. How to sequence therapies in Waldenström macroglobulinemia. Curr Treat Options Oncol. 2021;22(10):92.
87. Migkou M, Fotiou D, Gavriatopoulou M, Dimopoulos MA. Ibrutinib plus rituximab for the treatment of adult patients with Waldenström's macroglobulinemia: a safety evaluation. Expert Opin Drug Saf. 2021;20(9):987–95.
88. Castillo JJ, Kanan S, Meid K, Manning R, Hunter ZR, Treon SP. Rituximab intolerance in patients with Waldenström macroglobulinaemia. Br J Haematol. 2016;174(4):645–8.
89. Rossi D, Sciascia S, Fenoglio R, et al. Cryoglobulinemic glomerulonephritis: clinical presentation and histological features, diagnostic pitfalls and controversies in the management. State of the art and the experience on a large monocentric cohort treated with B cell depletion therapy. Minerva Med. 2021;112(2):162–74.
90. Henson JB, Sise ME. The association of hepatitis C infection with the onset of CKD and progression into ESRD. Semin Dial. 2019;32(2):108–18.
91. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med. 2017;377(15):1448–55.
92. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386(10003):1537–45.
93. Ghany MG. Current treatment guidelines of chronic hepatitis B: the role of nucleos(t)ide analogues and peginterferon. Best Pract Res Clin Gastroenterol. 2017;31(3):299–309.
94. Shah NJ, Aloysius MM, Sharma NR, Pallav K. Advances in treatment and prevention of hepatitis B. World J Gastrointest Pharmacol Ther. 2021;12(4):56–78.

95. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012;57(1):167–85.
96. Terrier B, Krastinova E, Marie I, et al. Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. Blood. 2012;119(25):5996–6004.
97. Argyropoulou OD, Pezoulas V, Chatzis L, et al. Cryoglobulinemic vasculitis in primary Sjögren's syndrome: clinical presentation, association with lymphoma and comparison with hepatitis C-related disease. Semin Arthritis Rheum. 2020;50(5):846–53.
98. Trejo O, Ramos-Casals M, García-Carrasco M, et al. Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. Medicine (Baltimore). 2001;80(4):252–62.
99. Saadoun D, Sellam J, Ghillani-Dalbin P, Crecel R, Piette JC, Cacoub P. Increased risks of lymphoma and death among patients with non-hepatitis C virus-related mixed cryoglobulinemia. Arch Intern Med. 2006;166(19):2101–8.
100. Boleto G, Ghillani-Dalbin P, Musset L, et al. Cryoglobulinemia after the era of chronic hepatitis C infection. Semin Arthritis Rheum. 2020;50(4):695–700.
101. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79(1):39–52.
102. Friedman MA, Curtis JR, Winthrop KL. Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2021;80(10):1255–65.
103. Lecrenier N, Beukelaers P, Colindres R, et al. Development of adjuvanted recombinant zoster vaccine and its implications for shingles prevention. Expert Rev Vaccines. 2018;17(7):619–34.
104. Scarpato S, Sebastiani M, Quartuccio L, Italian Group for the Study of Cryoglobulinaemia (GISC), et al. Provisional recommendations for SARS-CoV-2 vaccination in patients with cryoglobulinaemic vasculitis. Clin Exp Rheumatol. 2021;39 Suppl 129(2):149–54.
105. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum. 2010;62(1):75–81.
106. Richi P, Yuste J, Navío T, et al. Impact of biological therapies on the immune response after pneumococcal vaccination in patients with autoimmune inflammatory diseases. Vaccines (Basel). 2021;9(3):203.
107. Ferri C, Ursini F, Gragnani L, et al. Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. J Autoimmun. 2021;125:102744.