Review

Peripheral neuropathy in mixed cryoglobulinaemia: clinical assessment and therapeutic approach

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ABSTRACT

Peripheral neuropathy (PN) has been detected in up to 69% of patients with mixed cryoglobulinaemic syndrome (MCS). PN should be considered in any patient with sensory and/or motor signs and symptoms in the limbs. Electrodiagnostic tests are mandatory for the diagnosis of PN. Several different sets of diagnostic criteria have been created to assess it. All patients suspected of having neuropathy should undergo a nerve conduction study. A complete neurological evaluation at baseline and periodically should be done possibly by the same neurologists. The authors recommend rigorous scientific evidences that may help to obtain superior tools for accurate diagnosis and management of these conditions. Clinicians, armed with experience and recommendations, can find in this review data-driven guidelines to apply treatments of MCS and closely related disorders.

Background

Peripheral neuropathy (PN) has been found in up to 69% of patients with HCV-related mixed cryoglobulinaemic syndrome (MCS), with large variations in different studies (1-3). PN is also common in HCV-unrelated MCS reported in up 48.6% of cases described by the Italian Group for the Study of Cryoglobulinaemia (GISC) (4).

Recent reports suggest that cryoglobulinaemia (CG) may be a more common than previously thought cause of PN. In a prospective study of 100 patients with polyneuropathy or mononeuritis multiplex of unknown aetiology, after an initial workup, 11 were eventually diagnosed with cryoglobulinaemic neuropathy (CNP) (5). In another study of 100 patients with symmetric distal pain and negative examination, 16% of patients had elevated cryoglobulins (6). The results from these two reports suggested that even in the absence of purpura, CG may account for a substantial number of "idiopathic" neuropathies. The development of PN was unrelated to the HCV genotype. (3)

Sensory neuropathy, and in particular small fibre sensory neuropathy (SFSN), was significantly more common in the subgroup with the mild syndrome, whereas features of mononeuritis multiplex and sensory-motor neuropathy were almost exclusively associated with the active or severe MCS.

No significant correlation was found between the hepatopathy score, the liver enzymes, and the severity of NP (7).

Other distinctive features of CGN are female predominance, asymmetric distribution, and presence of sensory symptoms (1, 7-10). In 2012, the Peripheral Nerve Society (PNS) issued recommendations regarding the classification of vasculitic neuropathies and the diagnosis/treatment of non-systemic vasculitic neuropathy, including hepatitis C virus-related mixed cryoglobulinaemic vasculitis. The conclusion was drawn that the CNPs are usually caused by the vasculitis regardless of their phenotype (11).

The main symptoms of CNP are painful or burning paresthesias – often worse at night – in the lower limbs. The sensory symptoms usually precede the motor involvement (1). Electrodiagnostic studies previously showed that the PN is more common than the mononeuritis multiplex (12, 13), often in a subclinical form (14). In most patients, a distal symmetric sensory or sensory-motor PN was observed, while a mon-

oneuritis multiplex accounted for 12% of symptomatic patients. In particular, a small fibre neuropathy (SFN) tends to occur early in the course of CG and in patients with mild systemic disease. In a few patients, the neuropathy can be sensorimotor presenting with rapidly progressive course (15).

Electrophysiological studies suggested axonal damage possibly due to epineural vasculitis caused by immune complex deposition, with subsequent ischaemic pathology due to alterations in the blood flow (2). Cell-mediated damage is suggested by the finding of Th_1 cytokines and chemokines in the inflammatory vascular lesions (16).

Morphological features and mechanisms

HCV-associated neurologic involvement ranges from the sensory distal PN to the mononeuritis or mononeuritis multiplex. Sensory or motor impairment of one or more distal nerves is most frequent, with asymmetric loss of sensation and weakness reaching symmetry over time. Prevalence of sensory and motor PN in HCV infection was found between 9% and 10%, respectively (3, 14). The sensory predominant symmetrical PN is associated with perivascular infiltration of lymphocytes and monocytes in small-sized vessels. The mononeuritis multiplex, involving one or two not contiguous nerves, is usually more systemic and it is associated with inflammation of medium-size vessels with multiple inflammatory cells eventually accompanied with asymmetric vascular necrosis (6, 15).

The earliest mechanisms proposed to explain the neurologic manifestations in HCV-related MCS include:

i. vascular deposition of HCV RNA containing cryoglobulins;
ii.. direct viral invasion;
iii.perivascular inflammation (9).

Nerve biopsy typically demonstrated axonal degeneration with loss of myelinated axons (7). HCV RNA was detected in both skin and nerve biopsy samples in the presence of a vasculitis patterns (17, 18). The presence of HCV RNA was previously attributed to:

i. HCV endocytosis by endothelia cells through low-density lipoprotein receptors (18);
ii. HCV infection of epinevrial inflammatory mononuclear cells (19). This view was in agreement with previously reported detection of HCV replicative RNA in peripheral blood mononuclear cells of patients with MC (20);
iii.Vascular deposition of HCV genomic RNA trapped in the cryoprecipi tate (2) (Fig. 1).

Clinical assessment

Based on consensus expert opinion, a PN should be considered in any patient with a progressive symmetrical or asymmetrical PN or polyradiculoneuropathy in whom the clinical course is acute or relapsing and remitting or progressive, especially if there are positive sensory symptoms, proximal or distal weakness, areflexia with or without wasting, loss of sensation as tactile, vibration or joint position (21, 22).

Cerebrospinal fluid (CSF) examination and magnetic resonance imaging (MRI) of the spinal roots, brachial or lumbar plexus and nerve biopsy should be considered in cases of suspected chronic inflammatory demyelinating polyneuropathy (CIDP) or vasculitic neuropathy. Nerve biopsy, when indicated, should be performed in clinically and electrophysiologically affected nerves and it is usually the sural, but occasionally the superficial peroneal, or the superficial radial. Nerve biopsy indication remains feasible only in cases of suspected vasculitis especially if in the absence of systemic signs (23, 24).

Electrophysiological assessment

Electrodiagnostic tests are mandatory for the diagnosis of PN. Minor electrodiagnostic features could be any abnormality of median and sural nerve sensory action potentials, reduced sensory nerve conduction speed and F-wave chronodispersion. If the electrodiagnostic criteria for definite neuropathy are not met initially at diagnosis, it is worth repeating the electrodiagnostic testing in more nerves or at a later date during follow up (22, 25).

Several different sets of diagnostic criteria have been created for the assessment of PN.

These have been reviewed and are available on the European Federation of Neurological Societies (EFNS) website (http://www.efns. org). For the present needs of this review, we refer to EFNS and Peripheral Nerve Society (PNS) diagnostic criteria, both with high specificity for both research and clinical practice. Serial electrophysiological studies may need to be performed during the follow-up of the patients according to the clinical evidence (23, 25).

Diagnostic criteria are currently being developed for defining chronic PN, either axonal or predominantly demyelinating, by the Task Force of the PNS who were required to develop their own criteria based on consensus (23).

All patients suspected of having neuropathy should undergo a nerve conduction study (NCS). Bilateral motor conduction studies of median, ulnar, peroneal, tibial nerves, sensory conduction studies of sural, median, ulnar nerves are commonly performed. The data could be considered sufficient when at least 2 motor nerves and one sensory nerve are examined in the lower limbs and 2 motor nerves and 2 sensory nerves in the upper limbs. Partial conduction block is defined as previously reported by a reduction of compound muscle action potential by proximal stimulation of at least 50% in the lower limb and at least 30% in the upper limb. Temporal dispersion is defined by a lengthening of motor responses of at least 30% by proximal stimulation (26). PN may be classified demyelinating if fulfills the established EFNS/PNS criteria for CIDP, while it is classified as axonal if it does not fulfill the EFNS/PNS criteria for demyelination. Spontaneous muscle fibre activity on EMG is recorded as a sign of axonal damage in the presence of decreased response amplitudes on conduction studies (22, 23, 26, 27).

Neurological assessment

A complete neurological evaluation at baseline and periodically should be done possibly by the same neurologists over time. A great strength of the assessments is the availability of repeated measures. A complete neuro-

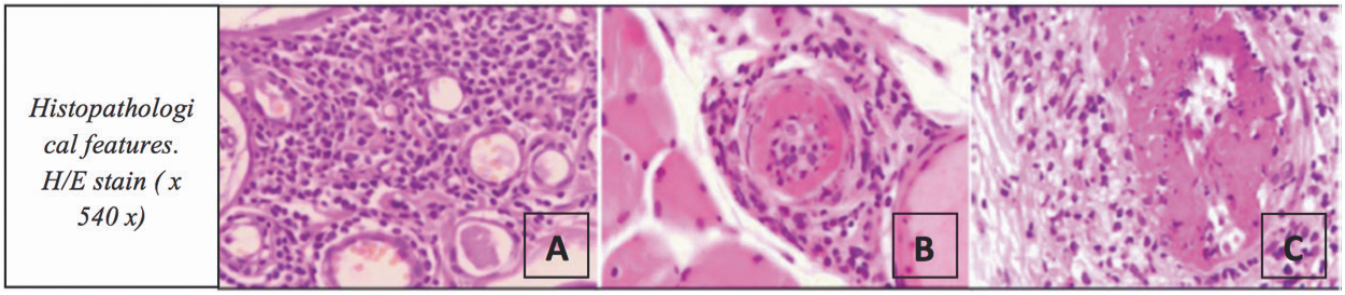

Fig. 1. Biopsies obtained from superficial peroneal nerves.
A: perivascular inflammatory cells from a patient with sensory-motor PN, with mild clinical disability on neurological score.
B: a small-sized vessel vasculitis (<80 um) often associated with endomysial inflammation in a patient with mononeuritis multiplex and moderate neurological disability. **C**: medium-sized vessel vasculitis (>80μm) in a patient with severe clinical symptoms and signs.

logic examination includes gait, muscle strength, trunk and limb coordination and full sensory testing at each visit. Patients are usually seen clinically every 6 to 8 months. Muscle strength evaluation includes scores obtained through manual muscle testing (MMT) according to the Medical Research Council (MRC) scale in 6 muscle pairs for each limb (score range 0–5, maximum possible 120) (25, 28).
Sensory function may be assessed by the Inflammatory Neuropathy Cause and Treatment (INCAT) sensory scale (ISS), which included pin prick, vibration two point discrimination (range 0–20) (22, 24-26). Disability is measured using the modified Rankin Scale (mRS) (range 0–5) and overall disability sum score (ODSS), which included functional description of extremity abilities (range 0–9) (25).

Clinical phenotypes of peripheral neuropathies

In synthesis, we can distinguish PN during MCS as:

Sensory neuropathies
The sensory PN including SFN are the predominant types. The involvement of sensory nerves may present with different patterns, resulting in distinct clinical phenotypes. A lesion of the dorsal root ganglia may cause a sensory ataxic neuropathy, while the involvement of the unmyelinated nerve terminals of the epidermis results in SFN.

Sensory axonal polyneuropathy
This PN presents with distal, symmetric sensory deficits in a *glove-stocking* distribution, and chronic or subacute onset. The lower limbs are initially affected and the deficits may spread proximally over the years as the PN worsens. In more severe cases, distal upper limbs may also be affected. The most common complaints are painful paresthesias in the feet. Deep tendon reflexes may be diminished, or absent in the affected limbs. The strength could be normal.
Nerve conduction studies typically reveal an axonal-type PN limited to the sensory nerves.
Nerve biopsy can show a varying degree of reduction in fibre density and is not helpful in the diagnosis except in cases with suspected vasculitis. Treatment is symptomatic. Tricyclic antidepressants, gabapentin, pregabalin, duloxetine, opioids and topical local anesthetics can be effective in softening the uncomfortable paresthesias (29, 30).

Sensorimotor axonal polyneuropathy
Patients with this type of PN initially complain of distal paresthesias and sensory deficits similar to those with the sensory neuropathy form. The sensory symptoms however are accompanied by gradual progression of muscle weakness in a distal, symmetrical distribution. The weakness is usually mild and limited to the foot extensors; rarely severe cases may require assisted ambulation. Deep tendon reflexes may be diminished or absent. Nerve conduction studies typically reveal an axonal PN affecting motor and sensory fibres (31).

Mononeuropathies and mononeuropathy multiplex
The clinical picture of mononeuropathy consists of sensory and/or motor deficits in the distribution of an innervations area of an individual nerve. Pain is common and the onset is acute or subacute as in cases of vasculitis. General symptoms may be present, as well as systemic manifestations of palpable purpura, suggesting a generalised vasculitis. Erythrocyte sedimentation rate and C-reactive protein levels are usually elevated. Electrophysiological findings could include an axonal pattern and "pseudo-conduction blocks" in an affected nerve. Nerve biopsy is indicated only to search for features of vasculitis: vessel wall damage, fibrinoid necrosis, mononuclear vascular or perivascular infiltrates can be found. Because the vasculitis could be a focal process, nerve biopsy may not reveal any changes, therefore, a combined nerve and muscle biopsy may increase diagnostic sensitivity up to 85% (Fig. 2).

Treatments

Symptomatic therapy
Neuropathic pain really needs an early treatment to reduce evolution towards a chronic condition.
It has been suggested that a low-antigen-content diet can improve symptoms, but it has not been analysed in more recent randomised studies (32).
NSAIDs are not recommended for prolonged use because of their hepatotoxicity and cardiovascular effects.
Recommended first-line treatments include various antidepressants (*i.e.* tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel alpha2-delta ligands (*i.e.* gabapentin and pregabalin), and topical lidocaine. Opioid analgesics and tramadol are generally recommended as second-line treatments. However,

these drugs may be considered for first-line use in selected clinical cases.

Anticonvulsants are useful for chronic neuropathic pain, especially when the pain is described as lancinating or burning. Gabapentin and pregabalin have the strongest evidence for the treatment of pain. These 2 "gabapentinoids" act as neuromodulators and they also have a peripheral analgesic action inhibiting selectively the response of C-fibres activated by inflammatory mechanisms (33-35).

Opioids were more effective than placebo for both the pain and functional outcomes of patients with nociceptive and neuropathic pain (36). The recommended front-line agents include hydromorphone, morphine, and oxycodone used orally on a time-contingent basis. An additional choice is the fentanyl patch for cases where the oral route is not an option (malabsorption, vomiting) or when it has failed. Morphine and meperidine are contraindicated in patients with liver involvement, whereas hydromorphone and oxycodone need only lower doses in these patients (36) (Fig. 3).

Antiviral therapy

Antiviral agents are the first choice in all HCV-related MCS. Until a few years ago Peg Interferon plus ribavirin was the best antiviral therapy. An improvement of neuropathic pain in HCV-positive patients was observed form 65.2% to 22.1% after Peg IFN and ribavirin therapy (37). The CIDP, reported in a minority of a HCV-infected population, significantly improved with IFNα and ribavirin therapy, although a few studies considered the neuropathy a side effect of PegIFNα (38). In these cases, intravenous immunoglobulin administration (IVIG) and plasmapheresis were effective in PN. The efficacy of ribavirin in improving the PN was attributed to its viral clearance, decreasing inflammation, circulating cryoglobulins and antimyelin associated glycoprotein (MAG) antibodies (39). Patients receiving interferon could experience side effects such as fatigue, flu-like symptoms, psychiatric symptoms, seizures, weight loss, symptoms of PN, and bone marrow suppression (40). However, studies of HCV-related PN treatment are lacking.

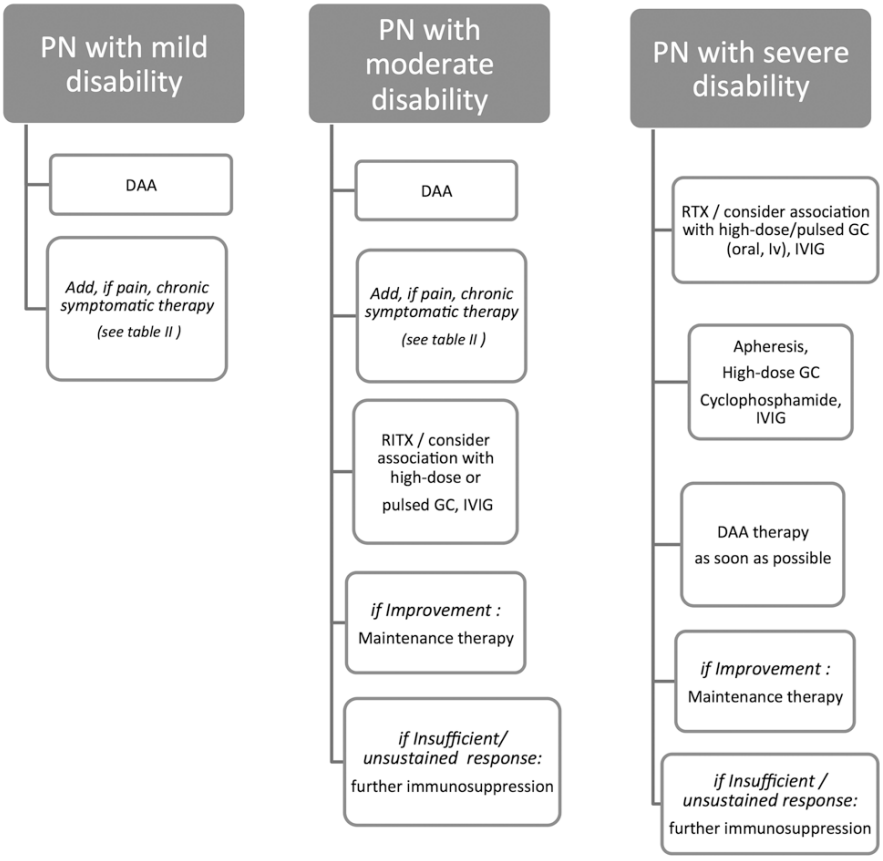

Fig. 2. Proposed algorythm of treatments of MCS related PN (sensory, sensory-motor, axonal or demyelinating) with confirmed diagnosis on clinical and electrophysiological grounds.
DAA: direct acting antiviral; RTX: rituximab; IVIG: intravenous immnunoglobulines; GC: glucocorticoid.

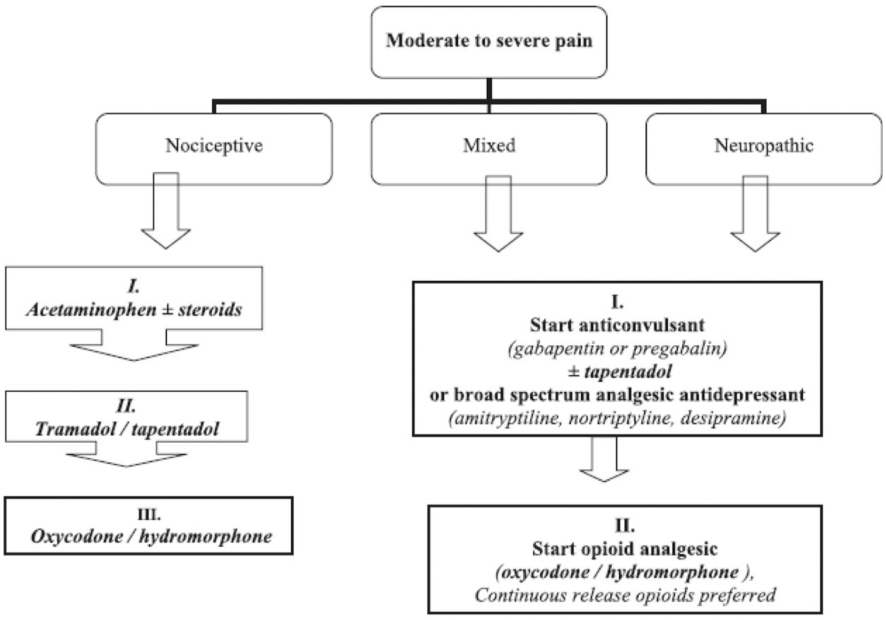

Fig. 3. Proposed algorithm of symptomatic therapy of painful NP (30).

In a Cochrane database systematic review only 10 studies were included (394 participants) regarding PN and HCV-related CG (41). Nowadays, it is accepted that Direct-Acting Antivirals (DAA) might be used in all cases of HCV-related MCS, but there are no guidelines dictated by a consensus ex-

pert opinion about DAA on PN and this is urgently needed (42). There are only anecdotal reports or studies limited to a few patients.

The available data suggest that even in patients with severe symptoms, treatment with DAA are associated with a significant improvement in the clinical picture in the majority of patients achieving a sustained viral response (43-49).

In the VASCUVALDIC study carried out by Saadoun *et al*., in 24 patients treated with Sofosbuvir plus ribavirin, PN improved in 15 out of 16 (94%) cases. The neuropathy total symptom score-6 (NTSS-6) decreased from 11.9±2.7 to 2.6±2.6. Motor symptoms slightly improved in 4 out of 8 patients (48).

In a recent study by Mazzaro *et al*. of 22 patients, 19 received a sofosbuvir-based regimen and three patients received other DAAs. PN was found in 10 cases (45%), after 48 weeks since the beginning of DAA, symptom relief of PN was observed in 7 (70%) patients at the end of therapy and remained in complete response at week 48, while three cases did not show any improvement of neuropathic pain and paresthesias. No improvement was detected in 30% of PN, therefore, they were considered as "non-responders" (50). These results are similar to those published by others (48).

Also, in 44 patients with HCV-associated CG vasculitis treated with DAA therapy, Gragnani *et al*. observed the persistence of sicca syndrome and of PN in 50% of the patients, suggesting that the irreversible damage of the salivary gland or of the peripheral nerves may be responsible for the lack of response (51, 52).

Overall, these results may be clinically useful for identifying patients who could need early and additional immunosuppressive treatment, such as rituximab (RTX) and/or plasmapheresis to avoid a permanent and irreversible PN that makes the patients non-responsive to treatments.

The study by Biasiotta (3) supported the theory that the development of PN was significantly associated with the duration of HCV infection, but it was unrelated to the duration of CG and the blood cryocrit level. This study showed that the amplitude of the sural-nerve sensory action potential (SAP), foot laser-evoked potentials, and the intraepidermal nerve fibre density were inversely correlated with the duration of HCV exposure, suggesting that the longer the duration of illness, the more severe the neuropathy would be (3).

Immunosuppressive drugs

The use of classic immunosuppressive agents such as glucorticoids and cytotoxic drugs was not recommended to manage CPN because of the associated viral infection (30). Immunosuppression prior to induction of antiviral therapy can be considered in patients with severe symptoms in order to obtain a reasonable and timely sustained therapeutic response (53). High-dose pulsed glucocorticoid therapy can be considered the first-line treatment of severe MCS (54)

Apheresis

A number of observations support the role of plasma exchange in improving acute renal disease and in treating PN (54). In a recent retrospective survey the authors recommended apheresis as an emergency treatment in such patients, also considering the absence of valuable alternatives (55). In this study PN was present in 54.7% of cases and was the most frequent clinical requiring apheresis treatment (55). There is some evidence that apheresis synchronised with the IVIG can be used to treat ulcers and CG-related PN, but this treatment may cause immunosuppression (56).

Rituximab

RTX is the only biological therapy proved to be beneficial in MCS, and should be considered when treating patients with severe clinical manifestations such as PN. RTX prior to induction of antiviral therapy can be considered in patients with severe symptoms to obtain a reasonable and timely therapeutic response (55, 58, 59).

In an open prospective study Cavallo *et al*. (60) assessed the drug effectiveness of RTX alone, evaluating electromyographic changes and laboratory parameters over at least 12 months. Sensory symptoms either disappeared or improved following the treatment with significant improvement in the neuropathy disability score. Electromyography revealed that the amplitude of compound motor action potential increased (60).

Roccatello *et al*. administered RTX to 26 patients with PN: complete remission of pretreatment active manifestations was observed in 80% of the cases (61).

De Vita *et al*. published a long-term, prospective, randomised controlled trial evaluating RTX therapy for cryoglobulinaemic vasculitis. Among the RTX-treated patients with PN, 11 of 16 responses were observed at 6 months, but a possible loss of response to RTX after month 6 was noted, and a second course of treatment with RTX was given to 6 of the 11 responders (62, 63).

Ferri *et al*. evaluated 87 patients with active cryoglobulinaemic vasculitis before RTX monotherapy and after 6 months by means of main clinical-serological parameters. A significant clinical improvement was observed in 44% of the PN, mainly paresthesias (64).

In several studies the advantage of RTX use was demonstrated in comparison to glucocorticoids, azathioprine or cyclophosphamide, or apheresis, by the primary end point of survival at 12 months, or by 6-month obtained remission in comparison to no therapy, or to glucocorticoids, or plasmapheresis (54, 65, 66).

To this end, no published studies clearly consider the evaluation criteria of PN in MCS both at the time of diagnosis and during a longitudinal follow-up. Homogeneous recommendations accepted by all the experts are needed to evaluate the degree of severity of MCS and the efficacy of the drugs or procedures used.

In fact, a wide consensus about the maintenance dosage and the frequency of RTX re-infusion has still not been reach. Moreover, the goals of antiviral treatment in patients with HCV-CV should be not only achieving SVR, but also symptomatic response of CV and minimisation of the use of immunosuppressive therapies (67).

Finally, the medication choice selection should be individualised to fully assess side effects, potential efficacy and comorbidities.

References

1. RAMOS-CASALS M, STONE JH, CID MC, BOSCH X: The cryoglobulinaemias. *Lancet* 2012; 379: 348-60.
2. FERRI C, LA CIVITA L, CIRAFISI C *et al*.: Peripheral neuropathy in mixed cryoglobulinemia: clinical and electrophysiologic investigations. *J Rheumatol* 1992; 19: 889-95.
3. BIASIOTTA A, CASATO M, LA CESA S *et al*.: Clinical, neurophysiological, and skinbiopsyfindings in peripheralneuropathyassociated with hepatitis C virus-relatedcryoglobulinemia. *J Neurol* 2014; 261: 725-31.
4. 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): S67-76.
5. FLETCHER NF, MCKEATING JA: Hepatitis C virus and the brain. *J Virol Hepat* 2012; 19: 301-6.
6. CACOUB P, POYNARD T, GHILLANI P *et al*.: Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. *Arthritis Rheum* 1999; 42: 2204-12.
7. GEMIGNANI F, BRINDANI F, ALFIERI S *et al*.: Clinical spectrum of cryoglobulinaemic neuropathy. *J Neurol Neurosurg Psychiatry* 2005; 76: 1410-14.
8. DURANTE-MANGONI E, IARDINO P, RESSE M *et al*.: Silent celiac disease in chronic hepatitis C: impact of interferon treatment on the disease onset and clinical outcome. *J Clin Gastroenterol* 2004; 38: 901-5.
9. BONETTI B, INVERNIZZI F, RIZZUTO N *et al*.: T-cell-mediated epinevrial vasculitis and humoral-mediated microangiopathy in cryoglobulinemic neuropathy. *J Neuroimmunol* 1997; 73: 145-54.
10. HSU JL, LIAO MF, HSU HC *et al*.: A prospective, observational study of patients with uncommon distal symmetric painful small-fiber neuropathy. *PLoS One* 2017: 12: e0183948.
11. COLLINS MP: The vasculitic neuropathies: an update. *Curr Opin Neurol* 2012; 25: 573-85.
12. TREJO O, RAMOS-CASALS M, GARCIA-CARRASCO M *et al*.: Cryoglobulinaemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine* (Baltimore) 2001; 80: 252-62.
13. NEMNI R, SANVITO L, QUATTRINI A, SANTUCCIO G, CAMERLINGO M, CANAL N: Peripheral neuropathy in hepatitis C virus infection with and without cryoglobulinaemia. *J Neurol Neurosurg Psychiatry* 2003; 74: 1267-71.
14. SANTORO L, MANGANELLI F, BRIANI C *et al*.: HCV Peripheral Nerve Study Group. Prevalence and characteristics of peripheral neuropathy in hepatitis C virus population. *J Neurol Neurosurg Psychiatry* 2006; 77: 626-9.
15. TAIEB G, MAISONOBE T, MUSSET L, CACOUB P, LEGER JM, BOUCHE P: Cryoglobulinaemic peripheral neuropathy in hepatitis C virus infection: Clinical and anatomical correlations of 22 cases. *Rev Neurol* 2010; 166: 509-14.
16. SAADOUN D, BIECHE I, MAISONOBE T *et al*.: Involvement of chemokines and type 1 cytokines in thepathogenesis of hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. *Arthritis Rheum* 2005; 52: 2917-25.
17. BONETTI B, SCARDONI M, MONACO S, RIZZUTO N, SCARPA A: Hepatitis C virus infection of peripheral nerves in type II cryoglobulinaemia. *Virchows Arch* 1999; 434: 533-5.
18. AGNELLO V, ABEL G: Localization of hepatitis C virus in cutaneous vasculitic lesions in patients with type II cryoglobulinemia. *Arthritis Rheum* 1997; 40: 2007-15.
19. BARBIERI D, GARCIA-PRIETO A, TORRES E, VERDE E, GOICOECHEA, LUNO J: Mixed cryoglobulinaemia vasculitis after sustained hepatitis C virological response with direct-acting antivirals *Clin Kidney J* 2019; 12: 362-4.
20. FERRI C, MONTI M, LA CIVITA L *et al*.: Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. *Blood* 1993; 82: 3701-4.
21. COMI G, ROVERI L, SWAN A *et al*.: The Inflammatory Neuropathy Cause and Treatment (INCAT) study group. A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. *J Neurol* 2002; 249: 1370-7.
22. LÉGER JM, VIALA K, NICOLAS G *et al*.: Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology* 2013; 80: 2217-25.
23. GALASSI G, TONDELLI M, ARIATTI A *et al*.: Long-term disability and prognostic factors in polyneuropathy associated with anti-myelin-associated glycoprotein (MAG) antibodies. *Int J Neurosci* 2017; 127: 439-47.
24. DALAKAS MC: Pathogenesis of immune-mediated neuropathies. *Biochim Biophys Acta* 2015; 1852: 658-66.
25. NIERMEIJER JM, FISCHER K, EURELINGS M *et al*.:Prognosis of polyneuropathy due to IgM monoclonal gammopathy: a prospective cohort study. *Neurology* 2010; 74: 406-12.
26. JOINT TASK FORCE OF THE EFNS AND PNS: European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the EFNS and PNS- First revision. *J Peripher Nerve Syst* 2010; 15: 1-9.
27. IANCU FERFOGLIA R, GUIMARÃES-COSTA R, VIALA K *et al*.: Long-term efficacy of rituximab in IgM anti-myelin-associated glycoprotein neuropathy: RIMAG follow-up study. *J Peripher Nerv Syst* 2016; 21: 10-4.
28. JOINT TASK FORCE OF THE EFNS AND THE PNS: "European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. *J Peripher Nerv Syst* 2010; 15: 185-95.
29. DWORKIN RH, O'CONNOR AB, BACKONJA M *et al*.: Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007; 132: 237.
30. SCARPATO S, ATZENI F, SARZI-PUTTINI P *et al*.: Pain management in cryoglobulinaemic syndrome. *Best Pract Res Clin Rheumatol* 2015; 29: 77-89.
31. SGHIRLANZONI A, PAREYSON D, LAURIA G: Sensory neuron diseases. *Lancet Neurol* 2005; 4: 349-61.
32. PIETROGRANDE M, MERONI M, FUSI A, AMATO M: Therapeutical approach to the mild cryoglobulinemic syndrome: results from a retrospective cohort study. *Ann Rheum Dis* 2006; 70: 65.
33. MORETTI R, CARUSO P, DAL BEN M, GAZZIN S, TIRIBELLI C: Hepatitis C-related cryoglobulinemic neuropathy: potential role of oxcarbazepine for pain control. *BMC Gastroenterol* 2018; 18: 19.
34. STAHL SM, PORRECA F, TAYLOR CP *et al*.: The diverse therapeutic actions of pregabalin: is a single mechanism responsible for several pharmacological activities? *Trends Pharmacal Sci* 2013; 34: 332-9.
35. CHEN SR, XU Z, PAN HL: Stereospecific effect of pregabalin on ectopic afferent discharges and neuropathic pain induced by sciatic nerve ligation in rats. *Anesthesiology* 2001; 95: 1473-9.
36. FURLAN AD, SANDOVAL JA, MAILIS-GAGNON A, TUNKS E: Opioids for chronic non cancer pain: a meta-analysis of effectiveness and side effects. *CMAJ* 2006; 174: 1589-94.
37. SOCKALINGAM S, ABBEY SE, ALOSAIMI F, NOVAK M: A review of sleep disturbance in hepatitis C. *J Clin Gastroenterol* 2010; 44: 38-45.
38. CACOUB P, TERRIER B, SAADOUN D: Hepatitis C virus-induced vasculitis: therapeutic options. *Ann Rheum Dis* 2014; 73: 24-30.
39. SANSONNO D, LAULETTA G, NISI L *et al*.: Non-enveloped HCV core protein as constitutive antigen of cold-precipitable immune complexes in type II mixed cryoglobulinaemia. *Clin Exp Immunol* 2003; 133: 275-82.
40. DUGUM M, O'SHEA R: Hepatitis C virus: here comes all-oral treatment. *Cleve Clin J Med* 2014; 81: 159-72
41. BENSTEAD TJ, CHALK CH, PARKS NE: Treatment for cryoglobulinemic and non-cryoglobulinemic peripheral neuropathy associated with hepatitis C virus infection. *Cochrane Database Syst Rev* 2014; 12: CD010404.
42. MONTERO N, FAVÀ A, RODRIGUEZ E *et al*.: Treatment for hepatitis C virus-associated mixed cryoglobulinaemia. *Cochrane Database Syst Rev* 2018; 5: CD011403.
43. 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: 1753-54.
44. SAADOUN D, RESCHE RIGON M, POL S *et al*.: PegIFNα/ribavirin/protease inhibitor combination in severe hepatitis C virus-associated mixed cryoglobulinemia vasculitis. *J Hepatol* 2015; 62: 24-30.
45. 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: 49-52.
46. 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: 575-83.

47. BASTYR EJ III, PRICE KL, BRIL V: Development and validity testing of the neuropathytotal symptom score-6: questionnaire for the study of sensory symptoms of diabetic peripheral neuropathy. *Clin Ther* 2005; 27: 1278-94.
48. 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: 1777-82.
49. COMARMOND C, GARRIDO M, POL S *et al*.: Direct-acting antiviral therapy restores immune tolerance to patients with hepatitis C virus-induced cryoglobulinemia vasculitis. *Gastroenterology* 2017; 152: 2052-62.
50. MAZZARO C, DAL MASO L, QUARTUCCIO L *et al*.: Long-term effects of the new direct antiviral agents (DAAs) therapy for HCV-related mixed cryoglobulinaemia without renal involvement: a multicentre open-label study. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S107-14.
51. GRAGNANI L, PILUSO A, URRARO T *et al*.: Virological and clinical response to interferon-free regimens in patients with HCV-related mixed cryoglobulinemia: preliminary results of a prospective pilot study. *Curr Drug Targets* 2017; 18: 772-85.
52. GRAGNANI L, VISENTINI M, FOGNANI E *et al*.: Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. *Hepatology* 2016; 64: 1473-82.
53. SHERIDAN DA, PRICE DA, SCHMID ML *et al*.: Apolipoprotein B-associated cholesterol is a determinant of treatment outcome in patients with chronic hepatitis C virus infection receiving anti-viral agents interferon alpha and ribavirin. *Aliment Pharmacol Ther* 2009; 29: 1282-90.
54. 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: 778-85.
55. 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: 639-45.
56. SCARPATO S, TIRRI E, NACLERIO C, MOSCATO P, SALVATI G: Plasmapheresis in crioglobulinemic neuropathy: a clinical study. *Dig Liver Dis* 2007; 39 (S1): S136-7.
57. 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: 444-54.
58. KOSMIDIS ML, DALAKAS MC: Practical considerations on the use of rituximab in autoimmune neurological disorders. *Ther Adv Neurol Disord* 2010; 3: 93.
59. QUARTUCCIO L, ZULIANI F, CORAZZA L *et al*.: Retreatment regimen of rituximab monotherapy given at the relapse of severe HCV-related cryoglobulinemic vasculitis: Long-term follow up data of a randomized controlled multicentre study. *J Autoimmun* 2015; 63: 88-93.
60. CAVALLO R, ROCCATELLO D, MENEGATTI E, NARETTO C, NAPOLI F, BALDOVINO S: Rituximab in cryoglobulinemic peripheral neuropathy. *J Neurol* 2009; 256: 1076-82.
61. ROCCATELLO D, SCIASCIA S, BALDOVINO S *et al*.: Improved (4 plus 2) rituximab protocol for severe cases of mixed cryoglobulinemia: a 6-year observational study. *Am J Nephrol* 2016; 43: 251-60.
62. 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: 843-53.
63. MENA-VÁZQUEZ N, CABEZUDO-GARCÍA P, FUEGO VARELA C, MANRIQUE-ARIJA S, FERNANDEZ-NEBROA A: Efficacy and safety of rituximab in vasculitic neuropathy: a systematic review of the literature. *Reumatol Clin* 2019; 15: 173-8.
64. 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* 2016; 11: 48-55.
65. FELDMAN L, DHAMNE M, LI Y: Neurologic manifestations associated with cryoglobulinemia: A single center experience. *J Neurol Sci*. 2019; 398:121-7.
66. SOARES CN: Refractory mononeuritis multiplex due to hepatitis C infection and cryoglobulinemia: efficient response to rituximab. *Neurologist* 2016; 21: 47-8.
67. MONTI S, BOND M, FELICETTI M *et al*.: One year in review 2019: vasculitis *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S3-19.