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8

Pain management in cryoglobulinaemic syndrome

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A B S T R A C T

Cryoglobulinaemic syndrome (CS) includes clinical signs and symptoms that range from the classic triad of Meltzer and Franklin (purpura, weakness and arthralgias) to multiple organ involvement, and it may be characterised by nociceptive or neuropathic pain. Both types of pain use the same pathways and neurotransmitters, but nociceptive pain has an adaptive system and biological function whereas neuropathic pain does not. Managing CS means dealing with often very different clinical patterns, activity and severity with the aim of preventing irreversible organ damage, reducing pain, improving the patients' quality of life and reducing social costs. However, treatment is still largely empirical, and it is often delayed. The Italian Group for the Study of Cryoglobulinaemia (GISC) strongly recommended a low-antigen-content diet and colchicine for all symptomatic CS patients. Patients with mild–moderate symptoms (such as purpura, weakness, arthralgia and initial neuropathy) have been treated with low or medium doses of steroids, and, in the presence of chronic hepatitis

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C virus (HCV)-related hepatitis, an attempt has been made to eradicate HCV with pegylated interferon plus ribavirin. In the case of severe or rapidly progressive disease (glomerulonephritis, neuropathy, leg ulcers, widespread vasculitis or hyperviscosity syndrome), more aggressive treatment should be used (e.g., high doses of corticosteroids, plasma exchange plus cyclophosphamide or rituximab). Pain management in CS therefore depends on the type of pain (nociceptive, neuropathic or mixed), the characteristics of the patients and their co-morbidities. Drug therapy should be carefully monitored in order to obtain prompt and beneficial results.

Introduction

Cryoglobulinaemic syndrome (CS) includes clinical signs and symptoms that range from the classic triad of Meltzer and Franklin (purpura, weakness and arthralgias) to multiple organ involvement (see Table 1), and it may be characterised by nociceptive or neuropathic pain [1,2]. Some of these symptoms, such as arthralgias/arthritis and peripheral neuropathy, are the preliminary classification criteria of cryoglobulinaemic vasculitis [2], and more than one mechanism involved in the chronic pain associated with CS may be responsible for different symptoms that act differently and show different changes over time from patient to patient.

Inflammation, which plays a role in nociceptive pain (e.g., articular involvement), can be expressed as 'somatic pain' activating bone, joint, muscle and connective tissue nociceptors, or 'visceral pain' when it stimulates afferent receptors in the deep organs. Neuropathic pain can be caused by a lesion in the peripheral nervous system (PNS): the damaged peripheral nerves are infiltrated by mast cells, granulocytes, macrophages and T lymphocytes, which contribute to the origin of neuropathic pain by secreting inflammatory mediators [3]. Furthermore, some inflammatory mechanisms and other

Table 1
Prevalence of clinical manifestations of cryoglobulinaemic syndrome.

Clinical manifestations	Prevalence
Purpura	73–100%
Weakness[a,b]	10–100%
Arthralgias[a]	33–91%
Non-erosive arthritis[a]	8%
Raynaud's phenomenon	7–40%
Sicca syndrome	10–51%
Peripheral neuropathy[b]	2–81%
Autonomic neuropathy[b]	Rare
Central nervous system involvement[b]	Rare
Nephropathy	8–54%
Endocrinological disorders	Rare
Liver damage	9–88%
Lung involvement	Rare
Visceral vasculitis[a]	Rare
Cardiovascular involvement	Rare
Leg ulcers[a]	4–30%
Spleen enlargement	4–50%
Lymphoadenopathy	16%
B cell lymphoma	11%
HCC (*Hepatocellular carcinoma*)	3%

[a] Nociceptive patterns of pain.
[b] Neuropathic patterns of pain.

neuropeptides may not only drive inflammation but also perpetuate neuropathic pain. Neuropathies generally affect the distal extremities with sensory or sensory/motor axonopathies, or mononeuropathy multiplex syndrome; demyelinating axonopathies are rare [4,5]. Finally, pain can be mixed: it may start as nociceptive pain and then change to neuropathic pain, or it may be due to the coexistence of articular and neurological damage.

Somato-nociceptive pain is usually localised to the site of injury, and it is often described as aching, squeezing, stabbing or throbbing. Visceral pain is poorly localised, and it is defined as cramping or gnawing pain. Neuropathic pain may be pyrotic, lancinating or burning, and it is associated with referred pain, allodynia, hyperalgesia and hyperpathia. Patients with neuropathic pain have a poor quality of life (QoL), and they suffer from sleep disorders, anxiety and depression, which can also lead to higher health care and social costs [6].

Neuropathic and nociceptive pain use the same pathways and neurotransmitters, but nociceptive pain has an adaptive system and biological function, whereas neuropathic pain does not. Chronic neuropathic pain is therefore defined as a specific disease due to persistent injury to the PNS and central nervous system (CNS), and so it is fundamental to recognise and treat earlier acute pain. Experimental models have shown that the development of sensitisation, wind-up, and CNS neuroplasticity is due to sensory stimuli acting on neural systems modified by past inputs, and that behavioural output is significantly influenced by the 'memory' of these events [7]. The use of neuroimaging methods has provided new insights into the aberrant cerebral processing of neuropathic pain. These mechanisms include the reorganisation of cortical somatotopic maps in sensory or motor areas, increased activity in primary nociceptive areas, the recruitment of new cortical areas usually not activated by nociceptive stimuli and aberrant activity in brain areas normally involved in descending inhibitory pain networks [8]. Consequently, the early treatment of neuropathic pain is necessary in order to block the enhancement of painful symptoms and their chronic evolution.

Peripheral neuropathy is one of the first major symptoms of patients with symptomatic CS, but its prevalence is unknown [9]. Electrophysiological studies have found peripheral neuropathies in 37% of patients, associated with CS, older age, higher levels of rheumatoid factor (RF) and immunoglobulin M (IgM), and low levels of C4 complement. However, the electrophysiological features of the peripheral neuropathies are unrelated to cryocrit levels or to the type of cryoglobulinaemia, and they are present in patients without any symptoms of cryoglobulinaemia other than pain and paresthesia. Furthermore, peripheral polyneuropathy may be associated with chronic hepatitis C virus (HCV) infection without mixed cryoglobulinaemia [10,11]: patients usually complain of sensory axonopathies or, less frequently, fulminating vasculitis, or mononeuropathy multiplex syndrome [12].

Finally, the clinical assessment of pain in CS needs to recognise the characteristics of the pain or types of pain that patients report.

The Italian Group for the Study of Cryoglobulinaemia (GISC) promoted a consensus conference to discuss the efficacy of currently used therapies with the objective of defining a core set of practical treatment recommendations on the basis of clinical trial data and expert opinion [13]. Managing CS means dealing with often different clinical patterns, activity and severity with the aim of preventing irreversible organ damage, reducing pain, improving the patients' QoL and reducing social costs; however, treatment is still largely empirical, and it is often delayed. Any therapeutic approach to CS should have four main objectives: to eradicate HCV; to limit or suppress B lymphocyte proliferation; and to limit and treat the vascular component (vasculitis), and to reduce the damage caused by circulating immune complexes [14]. Each of these therapeutic targets requires the use of different drugs or specific procedures, but only few randomised controlled trial (RCT) data concerning pain management.

Antiviral therapy

The GISC recommendations can be used to manage mixed CS and its aetiology [13]. The presence of cryoglobulins does not affect the response to antiviral treatment [15]. However, antiviral treatment is sometimes associated with major immune-mediated adverse events such as peripheral sensory/motor neuropathies [1,16–18], and there are no predictive factors to prevent them [1].

Biological therapy

It has been reported that rituximab (RTX) can improve or cure various clinical manifestations of CS, including fatigue, skin manifestations (purpura and skin ulcers), arthralgias and arthritis, and peripheral neuropathy (in about 75% of cases) [19,20]. Both sensitive and motor neuropathy improve within 1–5 months, leading to a stable or improved electromyographic picture [21–23].

Steroids

Glucocorticoids (GCs) are widely used to treat systemic vasculitis, and they have been prescribed at high doses (1–10 mg/kg) or in pulses to treat the critical manifestation of CS. Data from small case series support the effectiveness of high-dose pulse therapy in controlling disease flares [24,25]

- High-dose or pulsed GC therapy plays a substantial role in the management of critical patients with renal or neurological complications, or serious vasculitic manifestations (Evidence 4, C).
- The use of low–intermediate GC doses (0.1–0.5 mg/kg/day) has proved to be ineffective (Evidence 1b, A), but it has been reported that they improve the results of interferon (IFN) therapy (Evidence 1b, A).
- Chronic treatment with low GC doses should be avoided whenever possible and, in any case, be carefully monitored. Alternative therapies (colchicine, a low antigen-containing (LAC) diet) should be considered for maintenance treatment (Evidence 5, D).

Apheresis

A number of observations support the role of apheresis in improving acute renal disease and treating neuritis [26–28] and ulcers [24,26,29] (Evidence 4, C). There is some evidence that apheresis synchronised with the intravenous administration of high dose IGs can be used to treat ulcers and CS-related peripheral neuropathy, but this may also have a considerable immunosuppressive effect [29].

Cytotoxic drugs (methotrexate, azathioprine, cyclosporine A, and cyclophosphamide)

See the GISC recommendations concerning the management of mixed CS with cytotoxic drugs [13].

Colchicine

Colchicine has been proposed for the treatment of CS on the basis of its activity in reducing Ig secretion: colchicine at a dose of 1 mg/day improves purpura and pain (Evidence 4, C) after 6 months, and its prolonged use maintains the improvement and reduces the need for GCs (Evidence 3b, B) [30]. Its chronic administration seems to be useful in patients with mild CS, and, because of its good tolerability and few adverse effects, its use in all cases of CS is suggested provided that care is taken to monitor drug interactions:

(i) colchicine and cyclosporin may reciprocally increase each other's adverse/toxic effects (consider therapy modification) [31];
(ii) cyanocobalamin (vitamin B12) absorption may be decreased by colchicine, and it may lead to macrocytic anaemia or neurological dysfunction (consider vitamin B12 supplementation) [31];
(iii) colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a strong cytochrome P (CYP)3A4 inhibitor; in patients with normal renal and hepatic function, the colchicine dose should be reduced [32];

(iv) Colchicine may increase the serum concentration and myopathic (rhabdomyolytic) effect of 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors [33–35].

LAC diet

An LAC diet can improve phagocyte activity and modify the composition of immune complexes. CS patients who strictly follow such a diet experience a significant reduction in symptoms within 4–8 weeks. A chronic LAC diet has a steroid-sparing effect, reduces purpura and pain, is inexpensive and does not cause adverse effects [36,37].

Symptomatic therapy

Finally, GISC strongly recommended the need to manage pain, which often greatly affects the QoL of CS patients [13], but, unfortunately, this has not yet been considered in any controlled trial. Pain management in CS patients should therefore be individually tailored and based on drugs that have proved to be effective in controlling pain due to other vasculitides and neuropathies (Evidence 5, C). Interventions aimed at controlling any pain in CS patients should be attempted even during the administration of 'aetiological' treatments (Evidence 5, C). Moreover, pathophysiology and symptoms or signs may help to determine the most appropriate therapy, which may require combinations of medications and approaches.

Acetaminophen and non-steroidal anti-inflammatory drugs

The exact mechanism of action of acetaminophen is unknown, but it may include the donation of a moiety of endogenous cannabinomimetic and the activation of cannabinoid CB1 receptors in the CNS. Non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended for chronic administration because of their adverse effects, particularly hepatotoxicity [13].

Anticonvulsants

Anticonvulsants have been used to manage pain since the 1960s, and, together with antidepressants, they are one of the two most important adjunctive classes of pain medications [13]. The clinical impression is that they are useful for chronic neuropathic pain, especially when it is described as lancinating or burning. Gabapentin and pregabalin have the strongest evidence for the treatment of pain: these 'gabapentinoids' act as neuromodulators by selectively binding to the $\alpha 2-\delta$ subunit protein of calcium channels in various brain regions and the superficial dorsal horn of the spinal cord. They also have peripheral analgesic activity by selectively inhibiting the response of C fibres activated by inflammatory mechanisms [38]. These actions inhibit the release of excitatory neurotransmitters that are important in the production of pain.

Antidepressants

Antidepressants are as follows:

(i) Tricyclic antidepressants (TCAs, amitriptyline and nortriptyline) are useful means of controlling pain and reactive depression. Their exact mechanisms of action are unknown, but they may include norepinephrine and serotonin reuptake inhibition, and effects on H1 receptors, N-methyl-D-aspartate (NMDA) receptors and peripheral sodium channels. They are contraindicated in patients with ischaemic cardiopathy and conduction abnormalities. Trazodone is most tolerated by the elderly [13].

(ii) Selective serotonin–norepinephrine reuptake inhibitors (SSNRIs): duloxetine does not interfere with cardiac conduction or arterial pressure; venlafaxine does not have the sedative and antimuscarinic effects of tricyclic antidepressants, and it is more indicated in nephropathic than in cardiopathic subjects [13].

μ-Opioid receptor agonism and norepinephrine ± serotonin reuptake inhibition ('weak opioids')

(i) One-third of the activity of tramadol is due to μ-opioid receptor agonism and two-thirds to a mechanism similar to amitriptyline serotonin/norepinephrine reuptake inhibition. It is principally cleared by means of hepatic glucuronidation, weak protein binding and renal excretion. The doses and frequency of administration should be reduced in patients with liver and renal impairment. Seizures have been reported in the form of serotonin syndrome, and so patients with a history of seizures and those taking a TCA or SSRIs, a monoamine oxidase inhibitor, an antipsychotic drug, or other opioids may be at an increased risk of seizures [39].

(ii) Tapentadol is a novel, centrally acting analgesic with two mechanisms of action: μ-opioid receptor agonism and norepinephrine reuptake inhibition, which may contribute to its gastrointestinal tolerability. In patients with acute moderate–severe pain of various aetiologies, tapentadol immediate release (IR) offers comparable analgesia to that provided by oxycodone IR, with a lower incidence of adverse gastrointestinal effects and pruritus, and lower rates of discontinuation due to adverse effects. The analgesic effects of tapentadol are independent of metabolic activation, and tapentadol has no active metabolites [40]. Orally administered tapentadol is principally cleared by hepatic glucuronidation. Tapentadol does not undergo significant metabolism by CYP enzymes, and it does not inhibit or induce the activity of any of the CYP isoforms tested.

Opioids

There is growing evidence that controlled-release opioid analgesics can play a role in patients with chronic pain. A recent meta-analysis of 41 RCTs involving 6019 patients with nociceptive and neuropathic pain found that opioids were more effective than placebo in terms of pain and functional outcomes: only three side effects (nausea 14%, constipation 9% and somnolence 6%) were significantly more frequent than in the placebo-treated patients [41].

The recommended front-line agents include hydromorphone, morphine and oxycodone used orally on a time-contingent basis. Additional options include fentanyl patches when the oral route is not a reasonable option (malabsorption and vomiting) or has failed.

Morphine and meperidine are contraindicated in patients with impaired liver function, whereas hydromorphone and oxycodone only need to have their doses reduced. Moreover, in patients with renal impairment doses, the frequency of morphine administration should be reduced, and meperidine should be avoided; on the contrary, hydromorphone is safe to use [42].

Treatment plan

Before treating painful symptoms, it is very important to identify any co-morbidities (e.g., cardiac, renal or hepatic disease, depression and gait instability) that might be exacerbated by pain treatment or might require dose adjustments or additional monitoring, and that might explain the diagnosis and treatment plan to the patient in order to establish realistic expectations. It is also necessary to assess the pain and recognise its type.

The Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) recommends measuring pain intensity regularly. The most widely used and recommended scales of pain intensity include Scott–Huskisson visual analogue scales (VASs) or an 11-point numeric rating scale (NRS). During chronic pain assessments, the pain experienced during a medical examination may be different from usual pain, and so it is recommended to ask patients to measure their pain three times a day for 4 days [43].

The GISC strongly recommends an LAC diet and colchicine for all symptomatic CS patients [13]. Patients with mild–moderate symptoms such as purpura, weakness, arthralgia and initial neuropathy have been treated with low–medium steroid doses, and, in the presence of chronic HCV-related hepatitis, attempts have been made to eradicate HCV using pegylated IFN (PEG-IFN) plus ribavirin. In the case of severe or rapidly progressive disease (glomerulonephritis, neuropathy, leg ulcers,

widespread vasculitis or hyperviscosity syndrome), more aggressive treatment should be used (e.g., high doses of corticosteroids, plasma exchange plus cyclophosphamide or RTX) [13].

Nociceptive pain

Short courses of NSAIDs or, better, acetaminophen may be administered to control nociceptive pain in CS patients; in the presence of arthritis, low–medium steroid doses may be useful [13]. However, combined analgesic treatments (analgesic plus opioid) seem to be necessary in patients with severe pain (Evidence 5, D).

Neuropathic or mixed pain

Various scientific societies interested in chronic pain have issued guidelines for the treatment of neuropathic pain [44–46], indicating their preferences among first-, second- and third-line drugs (see Table 2). Symptomatic treatment can be started using a secondary-amine TCA (nortriptyline or desipramine) and/or a calcium channel $\alpha 2-\delta$ ligand (gabapentin or pregabalin); second choice is an SSNRI (duloxetine or venlafaxine).

For patients with acute neuropathic pain or episodic exacerbations of severe pain, and when prompt pain relief is required during the titration of a first-line medication, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies, and, subsequently, pain- and the health-related QoL should frequently be reassessed. If substantial pain relief is achieved (e.g., average pain reduced to $\leq$3/10) and the adverse effects are tolerable, the treatment can be continued; if only partial pain relief (e.g., average pain $\geq$4/10) is reached after an adequate trial, one of the other first-line medications should be added. If there is no or inadequate pain relief (e.g., <30% reduction) after an adequate trial of the target dose, the treatment should be changed to an alternative first-line medication. If trials of first-line medications alone or in combination fail, consideration should be given to second- and third-line medications or referral to a pain specialist or to a multidisciplinary pain centre (see Fig. 1).

Chronic pain in cirrhotic patients without renal failure

The main categories of pain medications (analgesics such as acetaminophen and NSAIDs, cyclooxygenase 2 (COX-2) inhibitors, anticonvulsants, antidepressants and opioids) are largely metabolised by the liver, but, unfortunately, there are no endogenous markers of hepatic clearance that can be used as a guide for drug dosing, and no readily available tests that accurately estimate the extent of residual liver function. There is a lack of high-quality, prospective data concerning the pharmacology and adverse effects of many analgesics in patients with advanced liver dysfunction [13].

The metabolites generally metabolise drugs by means of (1) oxidation, reduction or hydrolysis reactions of the hepatic CYP450 enzyme system; (2) conjugation to glucuronic acid, sulphate, acetate,

Table 2
Guidelines for neuropathic pain treatment.

Medication class	EFNS guidelines	NeuPSIG guidelines
Tricyclic antidepressants	First line	First line
Anticonvulsants (gabapentin and pregabalin)	First line	First line
SNRIs (duloxetine and venlafaxine)	Second line	First line
Topical lidocaine	If allodynia +	First line for localized NP
Opioid analgesics	Second/third line	Second line except in selected circumstances[a]
μ-opioid receptor agonism (tramadol and tapentadol)	Second/third line	Second line except in selected circumstances[a]

EFNS: European Federation of Neurological Societies; NeuPSIG: Neuropathic Pain Special Interest Group; SNRIs: serotonin and norepinephrine reuptake inhibitors (SNRIs); NP: neuropathic pain.

[a] Opioid analgesics and tramadol are considered first-line options for the treatment of acute NP, episodic exacerbations of severe NP, and during titration of a first-line medication in patients with substantial pain.

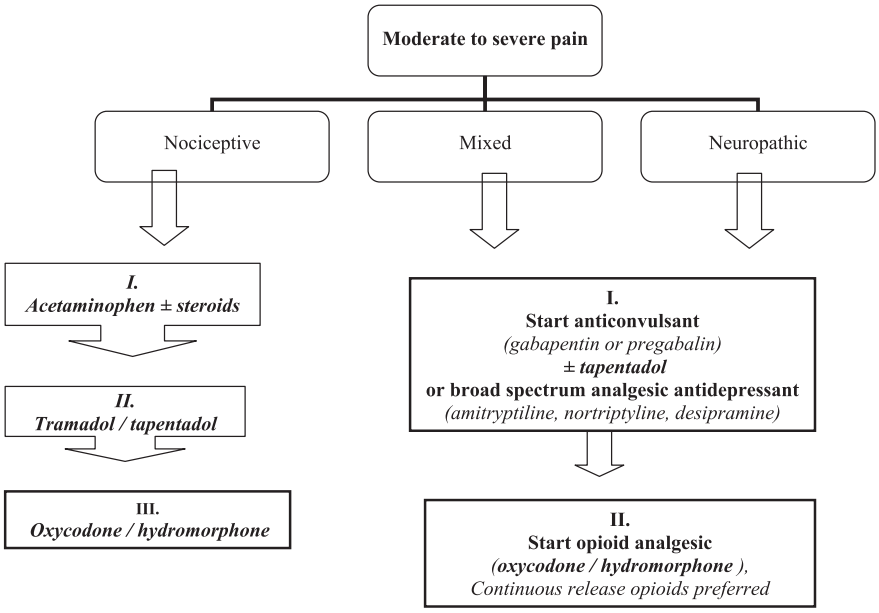

Fig. 1. Chronic pain treatment plan.

glycine, glutathione or a methyl group; and (3) biliary excretion and elimination. The pharmacokinetics of analgesic medications greatly depends on liver and renal function. Drugs with a high level of hepatic extraction (first-pass metabolism) such as morphine or fentanyl have a low level of bioavailability in healthy people but not in cirrhotic patients, whereas the bioavailability of drugs with a low level of hepatic extraction such as methadone is not affected by liver disease, although their hepatic clearance may be substantially altered. The ability to clear drug metabolites decreases with liver dysfunction, and cirrhosis alters the bioavailability of some parent drugs or metabolite(s) and increases toxicity; consequently, if these drugs are administered to cirrhotic patients, the dose should be reduced and/or the drug used less frequently [13].

Cirrhotic patients often have low serum protein and albumin concentrations. If a drug is highly protein bound, a low albumin level can lead to increased free drug levels and a consequent increase in adverse effects and toxicity. In patients with severe cholestasis, the clearance of drugs with a high level of biliary elimination such as buprenorphine may also be compromised because of dysfunctions in the basolateral and/or apical transmembrane transport systems of hepatocytes, thus requiring a dose reduction or drug avoidance.

Even the dosing of analgesic drugs that are mainly renally eliminated may require adjustment in patients with liver disease. The renal function of cirrhotic patients is often impaired despite normal serum creatinine levels because poor nutrition and reduced muscle mass lower the production of creatinine [42]. A pharmacological approach to analgesia in patients with CS and cirrhosis but without renal failure, active alcoholism or active substance abuse is shown in Fig. 2.

Chronic pain in patients with renal failure

The treatment of pain in patients with impaired renal function may be difficult, especially when opioids need to be used. In the presence of renal failure, significant metabolic and pharmacokinetic changes can lead to adverse reactions due to the accumulation of the parent compounds and active metabolites. Dosing analgesic drugs that are mainly eliminated renally may require adjustment depending on creatinine clearance and careful monitoring.

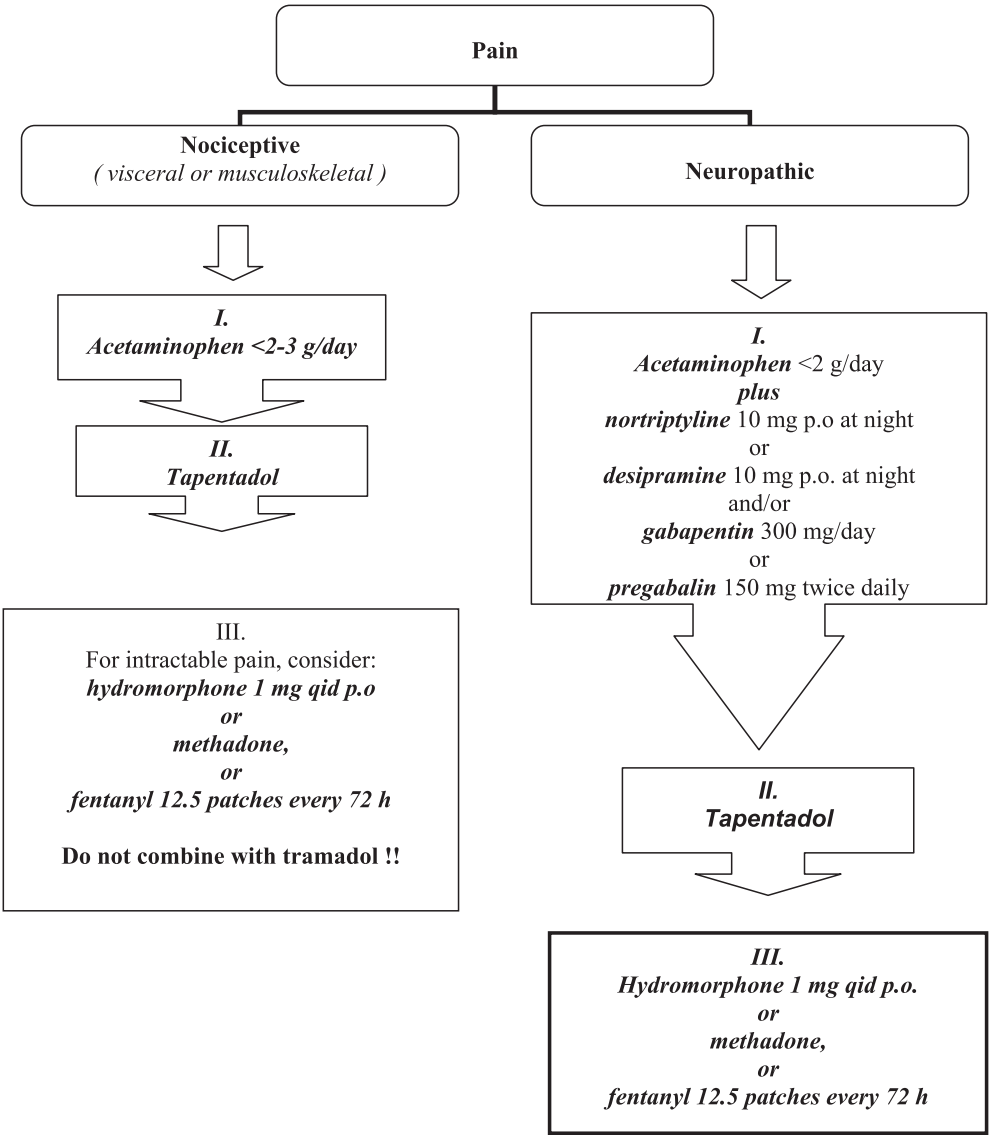

Fig. 2. Chronic pain treatment plan in cirrhotic patients without renal failure.

NSAIDs and colchicine should be avoided in nephropathic patients. Acetaminophen is recommended as the first step in the World Health Organization (WHO) ladder, followed by tramadol or, better, tapentadol (less problematic), although a dose reduction and increased dosing interval are necessary, and caution is required [47].

The half-lives of all opioids (except buprenorphine and hydromorphone) and their metabolites are increased in patients with renal dysfunction [48]. Morphine and codeine should be used very cautiously (and possibly avoided) in patients with renal failure and those on dialysis. Tramadol, hydromorphone, and oxycodone can be cautiously used, but they require close patient monitoring, whereas transdermal buprenorphine, methadone and fentanyl/sufentanil appear to be safe

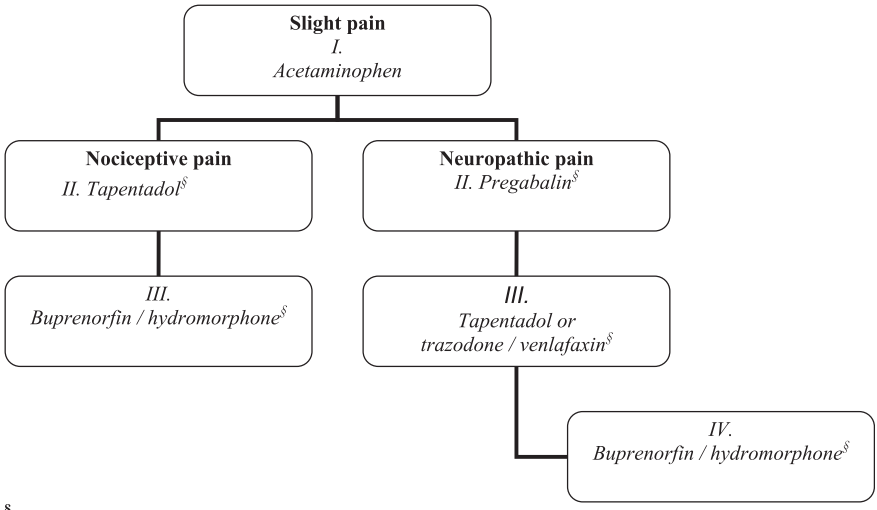

Fig. 3. Chronic pain treatment plan in patients with renal failure.

[49–51]. Hydromorphone may be safe and effective in selected haemodialysis patients [52] (see Fig. 3).

Chronic pain in older patients

Excretory organ (especially renal) function is frequently impaired in the elderly, and all NSAIDs, COX inhibitors, steroids and drugs with a long half-life are contraindicated in elderly patients with co-existing hypertension, diabetes and gastric disorders undergoing multiple drug therapies [13].

Patients with chronic pain and inadequate vitamin D levels require almost twice as much pain medication as those with adequate levels, and low vitamin D levels increase the likelihood of osteoporosis. Recommending vitamin D supplementation is therefore prudent, and it should be considered in older CS patients [53,54].

The half-lives of all opioids (except buprenorphine) and their metabolites are increased in the elderly, and so their doses should be reduced and there should be a longer time interval between doses; creatinine clearance should also be monitored (see Fig. 4).

The clinical relevance of the immunosuppressant effects of opioids in the elderly is not fully understood, and pain itself may also cause immunosuppression. However, in order to ensure adequate analgesia without significant adverse events, opioids with minimal immunosuppressive characteristics should be used. Although little is known about the immunosuppressive effects of most opioids, there is some evidence that they correlate with higher doses. Despite the very limited preclinical and clinical data, oxycodone, hydromorphone and buprenorphine seem to be safe in the elderly, whereas morphine and fentanyl should be avoided [55].

Drug interactions

As most CS patients are elderly and have a number of associated co-morbidities, attention should be paid to drug interactions, particularly in the case of ticlopidine, the macrolides, amiodarone, quinolone and calcium antagonists [56,57].

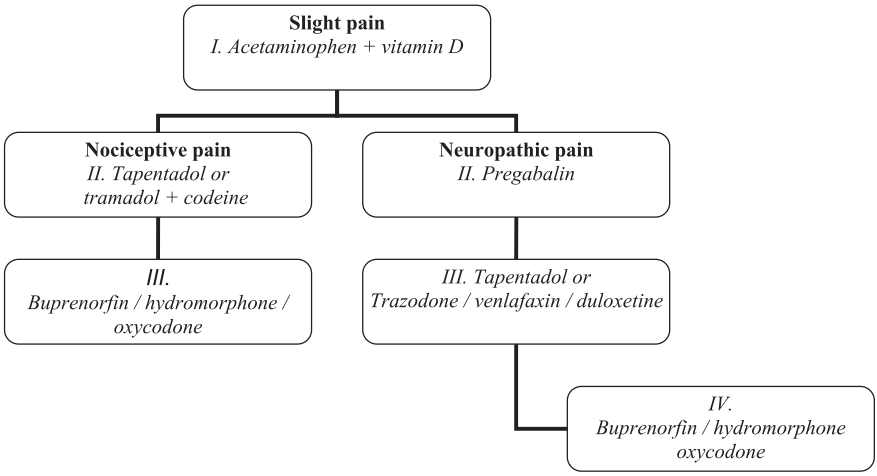

Fig. 4. Chronic pain treatment plan in older patients.

Physical chronic pain therapy

Transcutaneous electrical nerve stimulation (TENS) is only effective in treating peripheral neuropathic pain (level A) [43,58].

Summary

The GISC strongly recommend the need to manage pain, which often greatly affects the QoL of CS patients, but, unfortunately, this has not yet been considered in any controlled trial. Pain management in CS patients should therefore be individually tailored and based on drugs that have proved to be effective in controlling pain due to other vasculitides and neuropathies. Pathophysiology and symptoms or signs may help determine the most appropriate therapy, which may require combinations of medications and approaches as it depends on the type of pain (nociceptive, neuropathic or mixed), the characteristics of the patients and their co-morbidities. Drug therapy should be carefully monitored in order to obtain prompt and beneficial results.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Practice points

1. Pain is a symptom of CS, but it may be due to a mechanism related to neuropathic pain as well as the nociceptive pain associated with CS.
2. Inflammatory pain symptoms can be reduced by NSAIDs and biological and non-biological DMARDs
3. Identifying the type of pain is important for the management and treatment of patients with arthritides.
4. Optimal treatment needs to take into account symptoms such as pain and the overall quality of life, and it requires various approaches that include pharmacological analgesia and biological and non-biological treatments.

Research agenda

- To develop new laboratory and clinical indices to distinguish neuropathic and nociceptive pain in cryoglobulinaemia in order to reduce misdiagnoses
- To evaluate the adequacy and appropriateness of measures of diagnosing acute and chronic pain
- To develop new recommendations focused on pain in the context of cryoglobulinaemia syndrome

To promote future multi-centre studies and registries of pain in CS in order to improve the quality of life of patients and reduce overtreatment.

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