Review article

Anti-inflammatory therapies for pericardial diseases in the COVID-19 pandemic: safety and potentiality

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The COVID-19 pandemic is challenging our cardiovascular care of patients with heart diseases. In the setting of pericardial diseases, there are two possible different scenarios to consider: the patient being treated for pericarditis who subsequently becomes infected with SARS-CoV-2, and the patient with COVID-19 who develops pericarditis or pericardial effusion. In both conditions, clinicians may be doubtful regarding the safety of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, and biological agents, such as anti-IL1 agents (e.g. anakinra), that are the mainstay of therapy for pericarditis.

For NSAIDs, there is no clear scientific evidence linking ibuprofen and other NSAIDs to worsening of COVID-19; however, it seems prudent to continue them, if necessary to control pericarditis, and on the other hand, to prefer paracetamol for fever and systemic symptoms related to COVID-19. Treatments with corticosteroids, colchicine, and anakinra appear well tolerated in the context of COVID-19 infection and are currently actively evaluated as potential therapeutic options for COVID infection at different stages of the disease. On this basis, currently most treatments for pericarditis do not appear contraindicated also in the presence of possible COVID-19 infection and should not be discontinued, and some (corticosteroids, colchicine, and anakinra) can be considered to treat both conditions.

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Introduction

The Coronavirus disease-2019 (COVID-19) pandemic is challenging our cardiovascular care of patients with heart diseases. Growing evidence suggests that mortality and severe complications (e.g. sepsis, and cardiovascular or respiratory complications) are especially confined in elderly patients and/or those with underlying diseases.[1] In the setting of pericardial diseases, there are two possible different scenarios to consider: the patient being treated for pericarditis who subsequently becomes infected with SARS-CoV-2, and the patient with COVID-19 who develops pericarditis or pericardial effusion. In both conditions, clinicians may be doubtful regarding the safety of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, and biological agents, such as anti-IL1 agents (e.g. anakinra), that are the mainstay of therapy for refractory cases.[2–7]

At present, limited data have been published on cases with COVID-19 who develop pericarditis and pericardial effusion (Table 1).[8–11] Most reported cases have associated myocardial involvement with troponin elevation, another clinical manifestation of COVID-19. The aim of the present article is to review current data available on the safety of these treatments for patients with COVID-19 infection in order to provide guidance for proper clinical management of patients with pericardial diseases and suspected or established COVID-19 infection.

Mainstay of anti-inflammatory therapies in pericardial diseases

At present, NSAIDs are the mainstay of anti-inflammatory therapy of pericarditis either acute or recurrent together with the use of colchicine (Table 2).[5–7] In case of failure, intolerance or contraindication to NSAID or for specific indications (e.g. systematic inflammatory disease on maintenance therapy with corticosteroids), or clinical situations and concomitant diseases (e.g. pregnancy, renal failure, concomitant interfering therapies, such as oral anticoagulants), corticosteroids at low to medium doses (e.g. prednisone 0.2–0.5 mg/kg/day) are indicated as the second-line option in combination with colchicine.[2,12] In patients with refractory recurrent pericarditis, despite NSAIDs, corticosteroids, and colchicine, third-line therapies are recommended including intravenous human

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Table 1 Published cases with COVID-19 and pericarditis or pericardial effusion

Case	Clinical presentation	ECG/biomarkers	Specific therapy	Outcome
67 years, woman[8]	Hemorrhagic pericardial effusion with tamponade, dyspnea, orthopnea in a patient. No fever	Low QRS voltages, atypical ST/T changes; CRP elevation (15.9 mg/dl); late increase of troponin I (up to 2410 ng/l)	Colchicine, corticosteroids and hydroxychloroquine	Pericardiocentesis, no report on the detection of the virus in pericardial fluid
47 years, woman[9]	Hemorrhagic pericardial effusion with tamponade complicating myopericarditis. Chest pain and dyspnea. No fever	Sinus tachycardia, ST elevation in inferolateral leads, CRP not reported, Troponin T elevation (253 ng/l)	Not reported	Pericardiocentesis, no report on the detection of the virus in pericardial fluid
35 years, man[10]	Pericarditis with chest pain and high fever (39 °C)	ST segment elevation in inferolateral leads, CRP elevation (18.9 mg/dl) and normal troponin	Aspirin and colchicine (dosing not reported)	Remission in 9 days
78 years, man[11]	COVID-19 pneumonia presenting with chest pain and dyspnea with myopericarditis and mild pericardial effusion	AF, diffuse concave ST segment elevation, CRP (94.6 mg/l) and troponin T elevation (998.1 ng/l)	Betablocker, ACEI, diuretics	Not reported

COVID-19, Coronavirus disease 2019; CRP, C-reactive protein.

immunoglobulins,[13] azathioprine[14] or anti-IL1 (e.g. anakinra).[2–4] Anakinra, a nonselective anti-IL1 antagonist, has been especially studied in the setting of inflammatory recurrent pericarditis with fever and elevation of C-reactive protein at each recurrence and when colchicine is unable to control the disease and patients are unable to taper or stop corticosteroid (corticosteroid dependence).[3,4]

Coronavirus disease-2019 and nonsteroidal anti-inflammatory drugs

So far, no clear evidence has been reported on a link between NSAIDs and both respiratory and cardiovascular adverse effects, specifically in people with COVID-19[15,16]; accordingly there is no specific reason to advise against all use of NSAIDs in patients with COVID-19, when NSAIDs are indicated. Moreover, it is plausible that patients with higher fever and more severe disease might be the ones who will take more NSAIDs. Additional data are needed before a clear warning against the intermittent use of NSAIDs in the setting of COVID-19 infection. In our opinion, if NSAIDs are necessary to control acute pericarditis, they should be maintained. If they are taken to manage systemic symptoms possibly related to COVID infection, their use should be limited, and paracetamol considered first. At present, the European Medicines Agency (EMA) stated that there is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19. EMA is monitoring the situation closely and will review any new information that becomes available on this issue in the context of the pandemic.[16]

Coronavirus disease-2019 and corticosteroids

In the setting of COVID-19 infection, corticosteroids are used in order to suppress lung inflammation in advanced cases. The administered dose of methylprednisolone varied depending on disease severity. Although current interim guidance from the WHO on the clinical management of severe acute respiratory SARS-CoV-2 infection (released 13 March 2020) advises against the use of corticosteroids unless indicated for another reason (e.g. exacerbation of asthma or COPD, septic shock), risk/benefit analysis needs to be conducted for individual patients.[17] The WHO also recommends that clinicians considering corticosteroids for a patient with COVID-19 and sepsis must balance the potential small reduction in mortality with the potential downside of prolonged shedding of coronavirus in the respiratory tract as has been observed in patients with MERS. If corticosteroids are prescribed, it is recommended to monitor and treat hyperglycaemia, hypernatraemia, and hypokalaemia. The WHO suggests

Table 2 Current treatments for pericarditis and Coronavirus disease 2019 infection

Drug	Attack dose	Duration	LOE	Effect on COVID-19[a]
NSAIDs[2]	Aspirin 750–1000 mg × 3/day Ibuprofen 600–800 mg × 3/day Indomethacin 25–50 mg × 3/day	1–2 weeks but till symptoms resolution and CRP normalization	A	Harmful (?)[10,11]
Colchicine[2,5,6]	0.5 mg × 2/day (0.5 mg /day if <70 kg)	3 months (acute) 6 months (recurrent)	A	Potential therapy
Corticosteroid[2]	0.2–0.5 mg/kg/day of prednisone	Up to 1 month	B	Therapy for advanced cases[12]
Azathioprine[2,9]	Up to 2 mg/kg	>6 months	B	Unknown
NHIG[2,8]	400–500 mg/kg/day	5 days (can be repeated after 1 month)	B	Potential therapy
Anakinra[2–4]	2 mg/kg/day up to 100 mg/day	3–6 months then tapered	B	Potential therapy[12]

COVID-19,Coronavirus disease 2019; LOE, level of evidence for pericarditis; NHIG, normal human immunoglobulins; NSAID, nonsteroidal anti-inflammatory drugs: A for multiple RCTs or metanalyses, B for a single RCT or observational studies, C for expert consensus; CRP, C-reactive protein. [a] Current knowledge on the effect for COVID-19 infection, for corticosteroids and anakinra dosing for severe cases with COVID-19 is higher and intravenous: that is, methylprednisolone 1 mg/kg/day ivgtt for 7 days; anakinra intravenous infusion two to four times daily for 15 days. e.g. 400 mg/day in total, divided into four doses, given every 6 h or 5mg/kg twice daily, infused over 1 h.

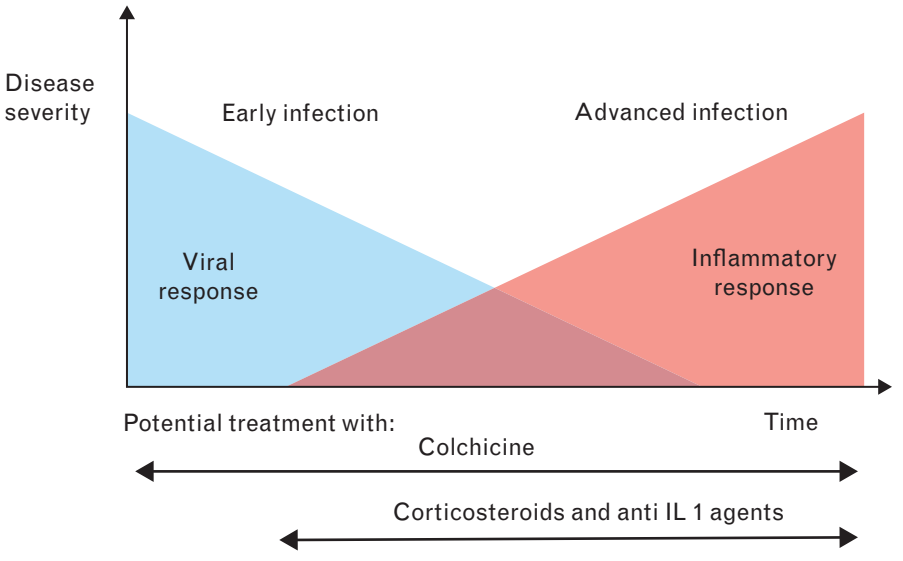
avoiding the routine administration of systemic corticosteroids for the treatment of viral pneumonia outside clinical trials.[17] Nevertheless, various studies in humans have also noted that corticosteroids may be effective in reducing immunopathological damage if utilized in the early acute phase of infection,[18] and in cases with fulminant myocarditis.[19–21] These observations challenge the previous recommendation of the 2015 ESC guidelines not to treat viral pericarditis with corticosteroids.[2] Indeed, in cases with prevalent immunopathological response triggered by viruses, these drugs could be useful and well tolerated. Currently, they are used in the clinical treatment of advanced cases of complicated COVID-19 pneumonia, and according to clinical experience, corticosteroids could be prescribed at the right time for the appropriate patient.[22,23] Moreover, results of several clinical trials involving corticosteroids will be soon available to provide more accurate evidence for or against their use. On this basis, if needed, corticosteroids could be used in patients with pericardial diseases and COVID-19 infection; moreover, they seem a potential treatment for more advanced cases of COVID-19 disease, when the host inflammatory response is predominant and harmful[23] (Fig. 1).

Coronavirus disease-2019 and colchicine

The use of colchicine for pericarditis was first proposed by Rodriguez de la Serna *et al.* in Barcelona in 1987 based on its efficacy in preventing polyserositis in patients with familial Mediterranean fever.[7] Colchicine has been empirically used for decades as an anti-inflammatory agent for the treatment of acute gout arthritis.[7] The drug is a microtubule-disrupting agent. It binds to tubulin, blocks mitosis, interferes with the transcellular movement of collagen, and stimulates, *in vitro*, the production of collagenase.[24] Moreover colchicine can interfere with the inflammosone and mitigate the inflammatory process. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is essential for the induction of this inflammatory state. Microtubules enable the necessary spatial arrangement of the components of the NLRP3 inflammasome in the cell, leading to its activation and propagation of the inflammatory cascade. Colchicine mediates its anti-inflammatory effect by inhibiting tubulin polymerization, and has been shown to attenuate macrophage NLRP3 inflammasome arrangement and activation *in vitro* and *in vivo* (Fig. 2).[25,26] Because of these composite effects, the use of colchicine has been advocated for the treatment of diseases characterized by prominent tissue inflammation or fibrosis, such as familial Mediterranean fever, Behcet's disease, pericarditis, atherosclerosis, and cirrhosis. The drug has the potential to be used either for prevention or treatment of inflammatory diseases. Moreover, colchicine has antiviral properties against flaviviridae, mouse hepatitis virus RSA59, and respiratory syncytial virus. Due to its anti-neutrophilic properties, colchicine was proposed as an antiviral agent and adjuvant treatment for RSV bronchiolitis.[27–29] Interestingly, colchicine was also able to suppress in-vitro infection of human Coronavirus NL63.[30] A rational of colchicine as an anti-HIV agent has been also proposed,[31] and microtubule disruption may influence SARS-CoV-2 viral genome replication.

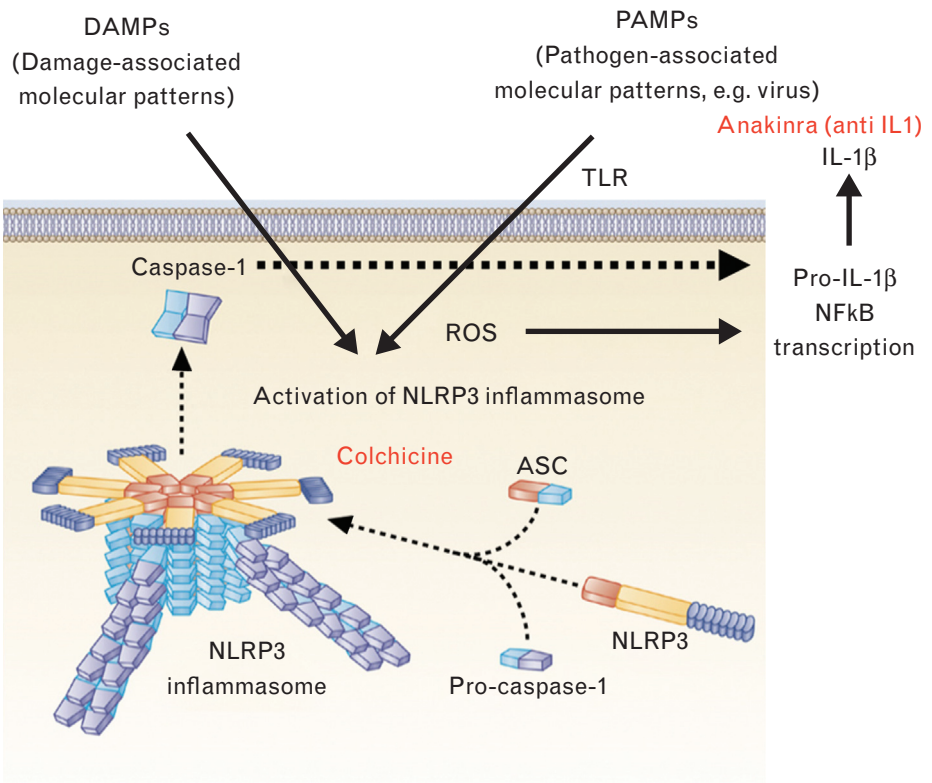
As the activation of the inflammosome and cytokine storm is a mechanism of progression and worsening of

Fig. 1



In Coronavirus disease 2019 infection, the early phase of infection is overcome by the majority of infected patients with the immune system response to the virus; however, in a minority of cases, the disease can progress to a second phase, characterized by prominent inflammation that can be treated with different drugs also used for pericarditis (e.g. colchicine, corticosteroids, anti-IL1 agents, such as anakinra).

Fig. 2



A simplified scheme of how the inflammasome is activated during pericarditis and Coronavirus disease-2019 infection with potential therapeutic mechanism of action of colchicine and anti IL1 agents (e.g. anakinra). The initial stimulus can be either microbial (PAMPs, e.g. virus) or sterile (DAMPs). This stimulus is then recognized by innate immunity receptors found either at the cell surface (TLRs) or inside the cell (NLRs). NLRs are then integrated into the structure of the inflammasome. TLR signalling leads to NF-kB activation and IL-1b production via reactive oxygen species (ROS). Colchicine blocks the intracellular assembly of the inflammosome preventing the generation of active IL1, whereas anti-IL1 agents (e.g. anakinra) act directly against IL 1.

COVID-19 respiratory infection, it can be anticipated that this drug can help lessen the progression of the disease.[32] At present, the use of colchicine is well established for pericarditis as it is a cornerstone of its treatment and prevention, whereas its use is anecdotal in the setting of COVID-19 infection and is under investigation in the early phases of the disease in nonhospitalized patients [Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA) (COVID-19; ClinicalTrials.gov Identifier: NCT04322682] as well as early treatment for hospitalized patients [Colchicine Efficacy in COVID-19 Pneumonia; ClinicalTrials.gov Identifier: NCT04322565, and The GReek Study in the Effects of Colchicine in Covid-19 cOmplications Prevention (GRECCO-19): ClinicalTrials.gov Identifier: NCT04326790]. Preliminary Italian experience on off-label use of colchicine in COVID-19 patients shows potential effect on mortality and reduction in the need for ventilation.[33] In addition, two Italian studies (ColCOVID 19 -EudraCT Number: 2020–001258-23, and COLVID-19- EudraCT Number: 2020-001475-33) have been approved by AIFA to investigate the efficacy and safety of colchicine in patients with COVID-19 infection. On this basis, the use of colchicine for pericarditis in COVID patients is not contraindicated and colchicine could become a treatment for the disease especially from early stages.

Coronavirus disease-2019 and anakinra

Anakinra is a nonselective IL 1 antagonist acting on both IL 1 alpha and beta receptors (Fig. 2). Advanced COVID-19 disease shares the phenotype of cytokine storm syndrome (CSS).[34] In the context of cytokine storm, the overproduction of IL-1 has a key role.[34] On this basis, currently the use of anakinra may be considered in advanced cases of COVID-19 as alternative to tocilizumab (IL-6 inhibitor),[35] and it is under active investigation in a clinical trial (Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection: ClinicalTrials.gov Identifier: NCT04324021). Currently, off-label use of anakinra is implemented as an alternative to tocilizumab in clinical settings with advanced COVID-19 infection in Italy.[36] On this basis, as for colchicine, the use of anakinra for patients with pericarditis and COVID-19

infection is not contraindicated and might become soon a new standard of treatment for advanced cases of the disease.

Conclusion

Although there is a warning on the use of NSAIDs in the setting of COVID-19 infection, which requires additional investigation, most treatments for pericarditis, including corticosteroids, colchicine, and anakinra do not appear contraindicated in the setting of COVID-19 infection. Nevertheless, when corticosteroids and anakinra are used, a careful monitoring of possible superimposed bacterial infections is warranted. On this basis, pericarditis treatments should not be discontinued in patients on treatment, when indicated to control the disease. As a matter of fact, these agents are currently being tested for efficacy in the setting of COVID-19 infection and could soon become part of the acknowledged treatment options.

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Conflicts of interest

M.I., A.B. and A.K. have been Advisory Board members for SOBI and Kiniksa. G.L. and Y.A. have been Advisory Board members for Kiniksa.

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