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Challenges in the management of patients with systemic light chain (AL) amyloidosis during the COVID-19 pandemic

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Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated coronavirus disease 2019 (COVID-19) is primarily manifested as a respiratory tract infection, but may affect and cause complications in multiple organ systems (cardiovascular, gastrointestinal, kidneys, haematopoietic and immune systems), while no proven specific therapy exists. The challenges associated with COVID-19 are even greater for patients with light chain (AL) amyloidosis, a rare multisystemic disease affecting the heart, kidneys, liver, gastrointestinal and nervous system. Patients with AL amyloidosis may need to receive chemotherapy, which probably increases infection risk. Management of COVID-19 may be particularly challenging in patients with AL amyloidosis, who often present with cardiac dysfunction, nephrotic syndrome, neuropathy, low blood pressure and gastrointestinal symptoms. In addition, patients with AL amyloidosis may be more susceptible to toxicities of drugs used to manage COVID-19. Access to health care may be difficult or limited, diagnosis of AL amyloidosis may be delayed with detrimental consequences and treatment administration may need modification. Both patients and treating physicians need to adapt in a new reality.

Keywords: amyloidosis, COVID-19, hydroxychloroquine, tocilizumab, remdesivir.

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A pandemic associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a major global challenge, causing a healthcare crisis even in regions with developed healthcare systems and access to advanced health technologies. A major shift of healthcare resources has been made towards the management of the pandemic. Mortality is higher amongst older people, morbidly obese individuals and those with comorbidities, but younger people without major underlying diseases may also develop severe disease.[1,2] Challenges associated with coronavirus disease 2019 (COVID-19) are greater for patients with chronic conditions: they are considered more vulnerable to the infection, while still need access to healthcare for the treatment of their underlying condition, in a situation of restricted resources. In addition, visiting hospitals may increase the risk of infection. Patients with malignancies were at increased risk, more likely to be diagnosed with COVID-19 and had a higher incidence of severe complications,[3–5] while in some studies recent cancer treatment further increased this risk, but not in others.[6]

Patients with light chain (AL) amyloidosis have an underlying usually low-grade plasma or B-cell malignancy causing their disease, and they receive chemotherapy,[7] thus being at higher risk of infections,[8] including from SARS-CoV-2, and probably at higher risk of severe COVID-19.[9] AL amyloidosis is a rare and challenging disease and the challenges may be even greater because special situations may go unnoticed or unattended amid the pandemic. It is difficult to gather data for the management of the infection, design specific interventions and predict the special challenges in the management of patients with AL amyloidosis, who have a multisystemic disease and are facing an infection with multiorgan complications. Finally, there is a perception in the medical community in general about the futility of treatment in advanced amyloidosis, a fallacy that remains persistent in the era of modern treatments, leading to difficulties in decision making for patients who become unwell with COVID-19. The International Society of Amyloidosis (ISA) has issued a short guidance for patients with amyloidosis during the pandemic and called for data collection.[10] In the present review, we attempt to describe potential challenges associated with the management of patients with AL amyloidosis during the SARS-CoV-2 pandemic.

The SARS-CoV-2 infection

SARS-CoV-2 invades the host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor followed by viral spike protein priming by host cell proteases including transmembrane protease, serine 2 (TMPRSS2).[11] SARS-CoV-2 primarily affects tissues expressing high levels of ACE2, including the lungs, the heart, the gastrointestinal tract (GIT) and kidneys.[12] COVID-19 is primarily manifested as a respiratory tract infection, but affects multiple systems including the cardiovascular, GI, kidneys, haematopoietic and immune.[13,14] In some patients, about 5–14 days from the onset of the first symptoms, a surge of clinical manifestations occurs with a pronounced systemic syndrome due to increase of inflammatory mediators and cytokines, characterised as 'cytokine storm'.[14–16] This can be associated with microvascular thrombosis of the lung and other vital organs.[17] Given the spread of the virus in multiple organs and the cytokines that cause a deregulation in tissue homeostasis, this disease may become rapidly fatal.

Special challenges for patients with AL amyloidosis

The diagnosis of amyloidosis requires an increased index of clinical suspicion in the setting of multisystemic disease. Given the non-specific nature of most symptoms, the diagnosis is often missed or delayed.[18] Some tests (including imaging, cardiac and renal biomarkers) can increase or set the suspicion of the disease, but the correct diagnosis depends on tests (biopsies, typing, genetic testing) that require expertise, and which may not be widely available.[7] In the context of the current pandemic many of the required resources (health personnel or imaging facilities) may not be available, be overwhelmed[19,20] or be difficult to get access to, leading to significant delays in establishing a correct diagnosis. In addition, there is a real risk that patients with less severe symptoms may defer seeking medical advice/care due to the fear of COVID-19, resulting in additional delays.

Patients with AL amyloidosis have multisystemic involvement, with different degrees of organ dysfunction and the clinical presentation in the case of COVID-19 infection may be more severe, while patterns of COVID-19 evolution may differ from other patients. In addition, therapeutic approaches for COVID-19 may be associated with special challenges. Table I presents the systems involved in AL amyloidosis and COVID-19, depicting the complexity of a potential infection in patients AL amyloidosis.

Most patients with AL amyloidosis have cardiac dysfunction of various degrees. Patients with COVID-19 and pre-existing cardiovascular disease are at increased risk of severe complications and death.[13,21,22] In addition, COVID-19 has been associated with cardiovascular complications.[13,21–23] Patients with AL amyloidosis and heart involvement have a limited reserve to cope with COVID-19-associated cytokine storm, due to autonomic nervous system involvement, heart failure with low cardiac output,[24,25] low albumin due to nephrotic syndrome that further enhances extravascular leak, all of which reduce the effectiveness of vasoconstrictors.[24] Patients with AL amyloidosis have a continuous loss of myocardial cells, as reflected by elevated troponin levels and pathology studies.[26] COVID-19 has also been associated with myocardial injury,[27] including cases of fulminant myocarditis with cardiogenic shock, as well as associated atrial and ventricular arrhythmias.[13,28] Hypoxia and electrolyte abnormalities are common in severe cases and further increase cardiac

Table I. Multisystemic involvement in patients with AL amyloidosis and COVID-19 infection and how may impact management of patients with both conditions.

	AL amyloidosis	COVID-19	Special challenges in patients with AL amyloidosis
Heart	• Involved in most patients • Major determinant of prognosis • Cardiobiomarkers (NTproBNP/BNP and cardiac troponins) define risk of early death • Risk of sudden death is very high among Stage 3B patients • Toxic free light chains can cause direct myocardial cell apoptosis, reflected by elevated cardiac troponin levels • Low arterial blood pressure is common and associated with worse prognosis • Most patients (especially with more sever cardiac amyloidosis) have very poor tolerance of standard drugs for heart failure • Paradoxical vasodilation may occur and is associated with risk of early death	• Cardiovascular complications are common in severe disease. • Myocardial injury,[27] including fulminant myocarditis with cardiogenic shock, • Associated atrial and ventricular arrhythmias.[13,28]	• Patients with SARS-CoV2 infection and pre-existing cardiovascular disease are at increased risk of severe complications and death.[13,21,22] • Poor tolerability of standard therapies for heart failure, such as β-blockers and ACE inhibitors in patients with AL amyloidosis. • Therapies such as hydroxychloroquine/chloroquine with or without azithromycin[13] have been associated with QT prolongation, risk of drug-induced torsades de pointes and drug-induced sudden cardiac death. • Risk of drug-induced arrhythmias can be amplified if multiple medications, which prolong QTc are combined. • Electrolyte abnormalities (hypocalcaemia, hypokalaemia, hypomagnesaemia) are common in AL patients and increase the risk of arrhythmias
Kidneys	• Nephrotic range proteinuria, associated with, low blood pressure, peripheral oedema and effusions • Urine loss of immunoglobulins • Increased thrombotic risk	• AKI is common among patients with severe COVID-19[49,23] • Proteinuria may develop in up to 43·9% of infected patients, especially those with AKI[50] • SARS-CoV-2 can be detected in the urine of patients with severe COVID-19.[49] • Co-expression of *ACE2* and *TMPRSS* genes in podocytes and proximal straight tubule cells, indicates that kidney is a target of SARS-CoV-2.	• Depleted intravascular volume and reduced vascular tone during cytokine storm may increase the risk of acute renal failure; • Mounting an immune response may also be inadequate with continuous loss of protective immunoglobulins • Dosing of several drugs may need be adjusted to degree of renal dysfunction. • Up to 50% of chloroquine and 15–25% of total clearance of hydroxychloroquine is done by the kidneys[52] • These drugs are not dialysable.[53] • Hydroxychloroquine is bound to plasma proteins[54] • For dialysis-dependent patients, measures to reduce COVID-19 risk in dialysis facilities should be followed.[57] • Patients with kidney transplants may be at higher risk of severe COVID-19
Peripheral blood	• Cytopenias are uncommon and associated with use of chemotherapy • The coagulation and fibrinolytic system are often deregulated due to sequestration of clotting factors and loss of fibrinolytic and anti-coagulation factors in urine	• Lymphopenia is common and associated with prognosis • Coagulation disorders are relatively common mostly among patients with severe disease: elevated D-dimers and their gradual increase are associated with poor prognosis.	• Thromboprophylaxis is highly recommended for hospitalised patients with COVID-19 • Thromboprophylaxis improve outcome • Thromboprophylaxis with LMWH or fondaparinux is suggested over

Table I. (*Continued*)

	AL amyloidosis	COVID-19	Special challenges in patients with AL amyloidosis
	• Small vessels may be dysfunctional due to amyloid deposition • Atrial arrhythmias predispose to cerebrovascular complications	• Disseminated intravascular coagulation (DIC) has been described other thrombotic complications have been reported as the cause of death in some patients.	unfractionated heparin to reduce contact unless the patient is judged to be at increased bleeding risk • In patients with AL amyloidosis with COVID-19 the use of thromboprophylaxis should be cautious with close monitoring due to increased bleeding risk.
Liver	• Hepatic involvement is common, but the clinical manifestations are usually mild; • Amyloid is deposited in the parenchyma, along the sinusoids within the space of Disse, or in blood vessel walls; compressing hepatocytes. • Symptomatic involvement, including rupture, portal hypertension or hepatic failure, is rare. Most common manifestations include hepatomegaly and increased cholestatic enzymes.	• Different degrees of liver dysfunction have been reported • Incidence of liver injury ranges from 20% to 78% in more severe cases, • Mechanisms for hepatic injury are unclear but ACE2 is expressed in bile duct epithelium more than hepatocytes • Usually presents with abnormal levels of aminotransferases, less often elevated bilirubin levels.[15,49,69] • Immune-mediated inflammation may contribute to liver injury in critically ill patients.[71]	• Limited data from China indicate increased risk of acute liver injury among patients with viral hepatitis during COVID-19.[49] • Cirrhotic patients may have higher risk of COVID-19 infection
GI	• Diarrhoea, constipation or alternating are commonly found • May be due to direct intestinal involvement or due to autonomic system involvement • Malabsorption, poor nutritional status and sarcopenia are common in more advanced involvement.	• SARS-CoV-2 binds to ACE2 and TMPRSS2 that are expressed in small intestine • ACE2 is expressed in the upper oesophagus and colon. • Viral RNA may be shedding in stool. • Diarrhoea is common; incidence rate of diarrhoea is 2–50%. • Diarrhoea may precede or present along with the respiratory symptoms.	• In patients with chronic diarrhoea, symptoms from GI associated with COVID-19 may evade • Patients at poor nutritional status and sarcopenia may be at higher risk to acquire infection and have worse prognosis when infected by SARS-CoV-2
Peripheral nerve	• Peripheral and autonomic neuropathy are common in patients with AL amyloidosis • Different types of peripheral neuropathy may occur depending on major symptoms and clinical findings • Symptoms of neuropathy may deteriorate during therapy with bortezomib or thalidomide.	• Limited data • In a retrospective series, 36·4% of the patients had neurological manifestations, mostly among patients with severe infection, • Acute cerebrovascular diseases, impaired consciousness and rhabdomyolysis were the most common • 8·9% had PNS symptoms, most common being taste and smell impairment. • The risk cerebrovascular complications seem to be increased in patients with COVID-19	• And this risk of cerebrovascular complications is increased in COVID-19 and AL amyloidosis, especially those with cardiac involvement who are at risk of atrial arrhythmias.

PNS, peripheral nervous system.

arrhythmia risk. There are limited data to understand these specific risks in the general COVID-19-infected population, even less in infected patients with AL amyloidosis. Monitoring of troponins may be useful, but the rise due to COVID-19 myocarditis in patients with AL amyloidosis needs to be interpreted in context of baseline levels that may already be increased. Most patients with AL amyloidosis are also receiving diuretics, placing them at increased risk of electrolyte imbalances, which may further trigger arrhythmias. The potential role of monitoring for arrhythmias (e.g. with telemetry) or additional pharmacological therapies or interventions (such as implantable cardioverter defibrillator) is unknown. Given the poor tolerability of standard therapies for heart failure, such as β-blockers and ACE inhibitors in patients with AL amyloidosis,[29] the management of arrhythmias during COVID-19 infection may be particularly difficult. The use of ACE inhibitors or angiotensin-receptor blockers is limited in patients with amyloidosis due to poor tolerance, but data do not support their discontinuation specifically for COVID-19.[30,31]

Therapies under investigation for COVID-19 have been associated with cardiovascular side-effects.[13] Hydroxychloroquine[32–34] with or without azithromycin[32] is used in many centres despite the lack of strong data, but this therapy has been associated with QT prolongation, increasing the risk of drug-induced *torsades de pointes* and drug-induced sudden cardiac death.[35,36] This risk can be further amplified if multiple medications that prolong QTc (i.e. azithromycin, lopinavir/ritonavir) are combined. For the general population, which needs to be assessed for the risk of QTc prolongation and further management, there is some guidance.[37] Baseline QTc status should be obtained and if >480 ms, in the absence of any drugs or factors prolonging QTc, may identify individuals at increased risk of QT-related ventricular arrhythmias. Patients with a resting QTc of ≥500 ms, due to any cause (drugs, electrolyte abnormalities etc.), have a greater risk of drug-induced arrhythmias; in such patients every effort should be made to correct electrolyte abnormalities (hypocalcaemia, hypokalaemia and hypomagnesaemia) and re-evaluate non-essential medication causing QTc prolongation. Closer monitoring should be considered, in the context of availability of such devices, staff and equipment protection and resources. The decision to start anti-COVID-19 therapy should depend on the risk–benefit ratio in each individual patient, but due to lack of data, clinical judgment is critical. Tocilizumab has been used in patients with COVID-19 during the cytokine storm phase, with some encouraging results.[38,39] It blocks the interleukin 6 (IL-6) receptor, a key cytokine during this phase of the disease; however, several more cytokines are critical. Tocilizumab has a proven safety profile during cytokine storm syndromes encountered in chimeric antigen receptor T-cell therapy[40] and has similar cardiovascular risk to other anti-rheumatic agents.[41] The risk of secondary bacterial and other opportunistic infections with tocilizumab in patients already on immunosuppressive chemotherapy remains unclear. Remdesivir has been evaluated in three studies.[42–44] and may be of some benefit in patients with moderate or severe COVID-19. In placebo-controlled studies severe toxicities were similar to placebo. Severe cardiac complications were uncommon and similar between groups. Most common complications included acute kidney injury (AKI), fever and increased aminotransferase levels. Remdesivir is given intravenously in a total volume of up to 250 ml, over 30–120 min, as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose for up to 10 days. Remdesivir in the treatment of COVID-19 is still under investigation, although its compassionate use has been approved. Remdesivir should be considered for patients with AL amyloidosis and COVID-19 as in any other patient with the infection, with close follow-up for potential cardiorenal and liver toxicity.

Patients with renal involvement due to AL amyloidosis lose large amounts of albumin in urine, leading to low osmotic pressure, low intravascular volume, low blood pressure, peripheral oedema and effusions, and are at increased risk of thromboembolic complications.[45–48] Often, they have hypogammaglobulinaemia due to urine loses of gamma-globulins further contributing to a immune-compromised status, while mounting an immune response may be inadequate. Beyond susceptibility to COVID-19, these patients may be more vulnerable to severe complications. It is more challenging to maintain intravascular volume and vascular tone in the case of cytokine storm, and they are at risk of acute renal failure. AKI is common among patients with severe COVID-19, ranging from 0·5%[49] up to 25%.[23] Data from China showed that 43·9% of SARS-CoV-2-infected patients, especially those with AKI, developed proteinuria,[50] while SARS-CoV-2 could be detected in the urine of patients with severe COVID-19.[49] Single-cell transcriptomic analysis of normal kidneys indicated that there is co-expression of *ACE2* and *TMPRSS* genes in podocytes and proximal straight tubule cells,[12] suggesting that the kidney might be a target organ for SARS-CoV-2. Thus, the risk of renal complications in patients with AL amyloidosis increases: a combination of direct viral insult with pre-renal complications due to a compromised circulatory system and pre-existing renal dysfunction may lead rapidly to renal failure and may portend a poorer outlook for renal function recovery. Dosing of many drugs may need adjustments due to renal dysfunction, including antibiotics, anti-coagulation and COVID-19-specific therapy. Chloroquine is excreted partly (up to 50%) by the kidneys; some acute effects in patients with severe renal dysfunction have been described,[51] but in the short term is relatively safe. About 15–25% of hydroxychloroquine is cleared by the kidneys,[52] which is not dialysable[53] and is bound to plasma proteins[54]; in nephrotic patients this may cause an additional challenge to predict efficacy and safety. Experience with remdesivir in patients with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73m^2 is limited. A significant proportion of patients with AL

amyloidosis require chronic dialysis, due to end-stage renal disease (ESRD); these patients have significantly worse outcomes than patients on dialysis for other indications.[55] Renal transplantation is increasingly used for the management of ESRD in patients with AL amyloidosis.[56] It may be preferable to defer planned organ transplantation due to increased risk immediately after transplantation with additional burden of immunosuppressive therapy. For patients with dialysis-dependent renal disease, measures to reduce the risk of COVID-19 in dialysis facilities should be followed.[57]

Patients with AL amyloidosis usually do not present with severe cytopenias, beyond those caused by chemotherapy. COVID-19 has been associated with certain haematological complications,[58] the most common being lymphopenia, which may have prognostic implications. Coagulation disorders are frequent in severe COVID-19: elevated D-dimers and their increase are associated with poor prognosis.[2,59,60] Disseminated intravascular coagulation requires prompt intervention; other thrombotic complications have also been reported as a cause of death. Thromboprophylaxis is recommended for hospitalised patients with COVID-19 and may be associated with better outcome. The American Society of Hematology (ASH) recommends that all hospitalised patients with COVID-19 should receive thromboprophylaxis with low-molecular-weight heparin (LMWH) or fondaparinux (suggested over unfractionated heparin to reduce contact), unless the patient is at increased bleeding risk.[6] However, in patients with AL amyloidosis the coagulation and fibrinolytic system may be already deregulated[61–63], while small vessels may be dysfunctional due to amyloid deposition:[64] a bleeding and a thrombotic diathesis co-exist. Thus, use of thromboprophylaxis in patients with AL amyloidosis with COVID-19 should be cautious and closely monitored.

Gastrointestinal involvement is common in AL amyloidosis, presenting with diarrhoea, constipation or alternating between the two, malabsorption, poor nutritional status and sarcopenia,[65] further increasing susceptibility to infections. Diarrhoea, a common symptom of COVID-19 was initially neglected; an incidence rate ranging from 2% to 50% of cases is reported.[66] Importantly, it may precede or present along with the respiratory symptoms. SARS-CoV-2 binds to ACE2 and TMPRSS2 that are expressed in the small intestinal epithelia and viral RNA may shed in feces.[67,68] A significant proportion of patients with AL amyloidosis of the GIT suffer from chronic diarrhoea, so this symptom may go unnoticed as an initial presentation of COVID-19. The management of diarrhoea is symptomatic and does not seem to be associated with severe complications per se. Liver involvement is common in AL amyloidosis, but the clinical manifestations are usually mild, including hepatomegaly and increased cholestatic enzymes; symptomatic involvement (rupture, portal hypertension, hepatic failure) is rare. Patients with COVID-19 may develop different degrees of liver dysfunction, with an incidence ranging between 20% and 78% in severe cases. Patients mainly presented with abnormal levels of alanine aminotransferase and aspartate aminotransferase accompanied by slightly elevated bilirubin levels.[15,49,69] The mechanisms for hepatic injury in patients with COVID-19 may include direct damage to bile duct epithelial cells expressing ACE2[70] and immune-mediated inflammation in severe COVID-19.[71] In patients with AL amyloidosis cholestasis predominates; it is unknown whether infection with SARS-CoV-2 can further deteriorate liver function.

Peripheral and autonomic neuropathies are common in AL amyloidosis and may be of different types.[72] There are limited data for neurological manifestations among patients with COVID-19. In a retrospective series from China, 36·4% of the patients had neurological manifestations, mostly in those with severe infection, and included acute cerebrovascular diseases, impaired consciousness and rhabdomyolysis; 8·9% had peripheral nervous symptoms, most common being taste and smell impairment.[73,74] The risk of cerebrovascular complications seems to be increased in patients with COVID-19, as they are also increased in patients with AL amyloidosis, especially those with cardiac involvement.

Treatment of AL amyloidosis during the COVID-19 pandemic

The therapeutic approach to a patient with AL amyloidosis is individualised based on risk assessment,[7,75] aiming for a rapid and sustained reduction and ultimately elimination of free light chains (FLCs), with limited risk of toxicity, by means of cytotoxic therapy targeting the plasma/B-cell clone. Additional adjustments to therapy may be required during COVID-19 pandemic. Chemotherapy causes immunosuppression, which varies for different agents and regimens. It has been hypothesised, that patients receiving immunosuppressors or immunomodulators might have a milder clinical presentation of COVID-19[14,76]; however, clinical data remains limited. Recent data from immunosuppressed patients from Italy, appears to suggest no increased risk of severe infections (three out of 700 children with liver transplants tested positive and none with severe disease)[77]; however, in adult patients with renal transplants morbidity and mortality were high.[78] Bortezomib and other proteasome inhibitors (ixazomib, carfilzomib) are associated with increased risk of viral infections (e.g. varicella zoster virus reactivation and perhaps cytomegalovirus).[79] Patients on bortezomib may also present with pulmonary infiltrates and fever due to hypersensitivity pneumonia,[80,81] and should be kept in the differential diagnosis when other infectious causes are excluded (including COVID-19). Immunomodulatory drugs (IMiDs) are also associated with increased risk of pulmonary infections and thrombotic complications,[82] as well as pneumonitis.[83] Cyclophosphamide causes B- and T-cell depletion, bortezomib and steroids are associated with lymphopenia. Daratumumab depletes NK cells, which are important for responses to viral infections, and has been associated

with an increased risk of viral and respiratory tract infections,[84–86] in combination with other agents this risk may be even higher. Cytotoxic and/or immunomodulatory therapy in a patient with AL amyloidosis who has been infected with SARS-CoV-2 should be discontinued until recovery (Table II).

AL amyloidosis is a deadly disease; delays in the diagnosis and initiation of therapy may be detrimental. There is no 'asymptomatic' AL amyloidosis and most patients are diagnosed due to symptoms and complications. Therapy should start upon confirmation of the diagnosis in almost all cases; very few will be asymptomatic and be diagnosed as part of monitoring for prior monoclonal gammopathy of undetermined significance (MGUS). Despite the pandemic, indications to start therapy should not change, especially in patients with heart involvement who are at increased risk of amyloidosis-related death, and which in most cases exceeds the risk of acquiring COVID-19. It is not possible to define the optimal balance between the need for treatment for AL amyloidosis and the potential risk of infection. There is significant geographical variation in the severity of the pandemic and in some areas the risk of acquiring the infection is low, so that there may be no need for modifications of therapy.

In patients with a good clinical status, without cardiac amyloidosis and with stable organ function, e.g. with isolated renal involvement, one must balance the risks of delayed therapy *versus* risk of infection, in the each phase of the pandemic. Patients with preserved organ function (low-grade proteinuria and preserved eGFR, low cardiac biomarkers) have the best chances to achieve a remission, improve organ function and avoid complications such as dialysis. However, a short delay for 4–6 weeks, until the pandemic is under control in the area and the local healthcare system adjusts, may be without significant consequences. Patients in relapse are often more 'stable' than newly diagnosed ones. In those with slow increase and relatively low levels of circulating FLCs, without heart involvement, the indications to start therapy are anyway unclear[87,88]: such patients could probably wait and avoid frequent hospital visits. Again, for patients with cardiac involvement delays to provide therapy should be cautiously considered.[87]

A common question that arises is whether the treatment should change to a regimen or schedule that reduces hospital visits. Many experts suggested that oral therapies may be used instead of intravenous (IV) or subcutaneous (SC) therapies given in the hospital, or change to regimens that require less frequent visits or even delaying or skipping doses.[9,89,90] These strategies are expected to reduce the exposure of vulnerable patients to hospital environment and other 'risk' contacts, while they save resources. However, these strategies cannot be applied to all patients with cancer and a potential risk–benefit assessment should be performed before deciding to change therapy or skip doses/visits. For patients with acute diseases, in which full therapy may be life-saving the treatment should probably not change. This is the case for newly diagnosed AL amyloidosis: a rapid disease control is required in most patients with the most effective and safe

Table II. Summary of suggestion for the treatment of AL amyloidosis during the pandemic.

The risk of acquiring the infection is not the same across different regions.
AL amyloidosis is a deadly disease; delays in the diagnosis and initiation of therapy should be avoided if possible.
Therapy for AL amyloidosis should start upon confirmation of the diagnosis with few exceptions.
Indications to start therapy should not change, especially in patients with heart involvement.
For low-risk patients, a short delay, until local control of the outbreak, may be reasonable.
In relapsing patients, with slow increase and relatively low levels of FLCs, without heart involvement, could probably wait and avoid frequent hospital visits.
Omitting bortezomib for MDex is not recommended, as a randomised study showed that BMDex is associated with faster and deeper responses and longer survival than MDex.
Using SC bortezomib instead of IV reduces toxicity and in-hospital time and may be delivered in outpatient setting.
Oral instead of IV cyclophosphamide has similar pharmacokinetics and efficacy.
Prophylactic growth factors might be considered in selected patients receiving potentially myelotoxic therapy.
Daratumumab should be given at lower volumes (500 ml) and in shorter time (90 min) after the first few infusions, provided that no major infusion-related reactions occurred.
Daratumumab discontinuation may be considered in patients in complete response or after 2 years of therapy.
Cannot substitute bortezomib with ixazomib, at least in previously untreated patients or those with severe cardiac involvement.
In patients with relapsed disease, ixazomib-based therapy is reasonable
There are no data to support any dose modifications of any of the oral anti-plasma cell drugs (IMiDs, ixazomib, alkylating agents).
In selected patients, who have achieved a satisfactory haematological response and/or organ response, earlier completion of therapy or a less intensive schedule may be reasonable.
Steroid dose can be reduced or discontinued in patients on long-term lenalidomide.
If HDM/ASCT is planned, delaying or deferring the transplant may be a safer approach.
Hospital visits for follow-up evaluation should be reduced to those necessary, depending on local conditions and standards. Using local laboratories may be feasible in some areas.
Specialised testing can be usually postponed for stable patients in haematological remission and reserved for those in which a major treatment decision needs to be made.
Home measurement of weight, pulse rate and blood pressure should be encouraged and can be helpful to manage heart failure in many patients.
Telemedicine may be helpful, but has major limitations in a rare and complex disease such as AL amyloidosis.

therapy, and for some patients optimal anti-AL amyloidosis therapy should start even in the midst of the outbreak, e.g. for patients with cardiac involvement. Treatments for AL amyloidosis have not been developed in the context of multiple randomised studies, thus, we have limited data to propose one therapy over the other or assess the importance of full *versus* reduced dosing of critical drugs such as bortezomib or daratumumab, and no data to support changing an IV/SC drug for an oral drug. A randomised study showed that the combination of SC/IV bortezomib with oral melphalan and dexamethasone (BMDex) is associated with faster and deeper response than oral MDex; thus, avoiding bortezomib to keep only MDex may be associated with inferior outcomes in patients with previously untreated AL amyloidosis.[91] Minimising unnecessary visits and delays may be feasible and safe without compromising efficacy. Using SC bortezomib requires minimal time in the infusion centre and can be done in an outpatient setting; oral instead of IV cyclophosphamide has similar pharmacokinetics and efficacy.[92,93] Although cyclophosphamide, bortezomib, and dexamethasone (CyBorD/VCD) and BMDex pose low risk of neutropenia (although higher for BMDex), full blood count monitoring to reduce chemotherapy dose or provide prophylactic growth factors might be considered in selected patients. To reduce time of infusion and avoid excessive fluid, daratumumab should be given at lower volumes (of 500 ml), also allowing infusion in reduced time (in 90 min). This strategy can be employed after the first few infusions, provided that no major infusion-related reactions occurred.[94] Given that daratumumab was given for a fixed duration in prospective studies,[85,86,95] discontinuation may be considered in patients in complete response (CR) or after 2 years of therapy. Due to the lack of direct comparison it is difficult to propose substituting ixazomib for bortezomib, at least in previously untreated patients or those with severe cardiac involvement. However, ixazomib may be an option for some selected patients or be an alternative for those already on bortezomib who have achieved a response, in a heavily affected area. However, in the relapsed setting ixazomib-based therapy is a reasonable choice for patients with or without prior exposure to bortezomib.[96] There are no data to support any dose modifications of any of the the oral anti-plasma cell drugs during the pandemic (Table II).

For selected patients who have achieved a satisfactory haematological response (e.g. CR or very good partial response or even partial response with organ response), the treating physician may discuss whether to complete therapy earlier or continue with a less intensive schedule (e.g. reduce weekly to bi-weekly bortezomib). Steroid dose can be reduced or discontinued in patients on long-term lenalidomide, supported by data in myeloma.[97] If high-dose melphalan followed by autologous stem cell transplantation (HDM/ASCT) is planned, delaying or deferring the transplant may be a safer approach.[58] HDM/ASCT requires hospitalisation, may require intensive care for management of complications in some patients, blood and platelet transfusions and causes severe immunosuppression. In addition, there are no randomised data to support superiority of transplant over modern conventional-dose therapies in patients with AL amyloidosis; deferring transplant may also be an option.[98,99]

Enrolment in clinical trials has been affected by the pandemic; some have temporarily held enrolment or modified visit schedules to essential ones, without compromising patient safety and data integrity. However, clinical trials are critical for the development of new therapies for AL amyloidosis and patients should be encouraged to participate.

Following the patients with AL amyloidosis remotely

Hospital visits should be reduced to those necessary, thus, depending on specific local conditions and standards, local laboratories may be used to follow blood and urine parameters, as in other haematological malignancies.[100] Shipping tissue samples to referral centres for typing can reduce the need for travelling. Blood samples for measurement of FLCs, *N*-terminal prohormone B-type natriuretic peptide (NTproBNP) or troponin levels are rather stable if shipped overnight. Specialised testing can be usually postponed for patients in haematological remission and stable condition and reserved for those in which a major treatment decision needs to be made. Home collection of blood samples could be used, if this service is available, with appropriate social distancing measures; in our practice this has been an option that many patients accept. Simple measures like home measurement of weight, pulse rate and blood pressure can allow for meaningful discussion for management of heart failure in these patients. Telemedicine may be helpful, but one needs to take into consideration certain limitations of the distant physician–patient contact; in a rare and complex disease such as AL amyloidosis direct assessment from specialised experienced physicians may be critical.

Prophylactic measures for patients with AL amyloidosis during the pandemic

There is no vaccine or drug to use as prophylaxis for COVID-19. The most effective prophylactic measure is social distancing, isolation of those at risk of severe complications, and strict hygiene rules to reduce the virus transmission rate. There are no specific measures that patients with AL amyloidosis should follow to prevent COVID-19. Vaccination against influenza and pneumococcus should be continued, as these two diseases are common and may be lethal. There are no data to support screening for COVID-19 in patients with malignancies, including with AL amyloidosis. Local guidelines should be followed; however, the threshold to test a patient with AL amyloidosis in case of suspicion of COVID-19 should be low, due to the potential risk of rapid clinical deterioration in those with multisystemic amyloidotic

involvement. Polymerase chain reaction (PCR) testing is the current standard for the diagnosis of acute infection.[101] It is expected that valid serological tests will become available, that will detect specific antibodies to SARS-CoV-2 allowing the detection of past or relatively recent infection; however, there are no data regarding the immune status against the virus based on these tests. If a vaccine becomes available, patients with AL amyloidosis should be considered for vaccination, as with other standard vaccines, taking into account its safety and efficacy. Whether patients on daratumumab, bortezomib or rituximab will mount an immune response to the virus, or develop an adequate immune response to vaccination, is unknown and should be prospectively studied.

Many patients with AL amyloidosis are already on antivirals (acyclovir, valacyclovir etc.) as prophylaxis due to therapy with proteasome inhibitors or daratumumab, but, have no activity against SARS-CoV-2. Prophylactic antibiotics are often given either for prophylaxis (such as quinolone antibiotics[102]) or for their potential anti-fibril activity (doxycycline[103]). These drugs have no effect on COVID-19, but may reduce the risk of other infections and in the current context should probably be continued. In patients with AL amyloidosis presenting with fever and symptoms of respiratory infection, especially if they test negative for COVID-19, are still at significant risk of a bacterial or other viral (e.g. influenza) infection, which should not be overlooked. There are limited data to support the use of prophylactic immunoglobulins outside the context of severe hypogammaglobulinaemia with repeated infections. SARS-CoV-2 is a new virus and there is no population immunity and anti-SARS-CoV-2 antibodies are not expected to exist in immunoglobulin products. Convalescent plasma from patients previously infected with COVID-19 and recovered donors could offer passive immunity in some selected patients and is under investigation.

Access to healthcare for patients with AL amyloidosis developing SARS-CoV-2 infection

Most healthcare systems have made major adjustments to routine patient care to allow for high influx of patients presenting with COVID-19 infection. The access to monitored beds and intensive care units (ICUs) may be limited. The outcomes of patients with significant multiorgan damage in ICUs are poor. In the current climate, where every ICU bed has become a precious resource, the best utilisation for patients with multiorgan AL amyloidosis and severe COVID-19 infection remain unknown. In each case, the care must be individualised – a renal AL amyloidosis patient with good potential long-term outcome should be a good case for full care. Early discussion about resuscitation status with the patient and family with realistic assessments of outcomes is important to avoid difficult decisions when patients are admitted with COVID-19 and may not have access to supportive family.

Conclusions

COVID-19 is an ongoing pandemic with data changing continuously, and new information acquired with a speed never seen before. Still, prospective data are scarce. For patients with a rare disease such as AL amyloidosis, it is even more difficult to collect information on a large scale and make informed decisions. Ongoing data collection, observations and single case reports are all critical, as it is expected that the end of the pandemic is not close. At this date >600 clinical trial are registered in clinicaltrials.gov for COVID-19. As there are limited data for this disease, we urge the enrolment of patients in clinical trials. The ISA drives an initiative to collect data of patients with amyloidosis with COVID-19; ASH is also gathering data for patients with haematological diseases and COVID-19, including patients with AL amyloidosis.

Given the multisystemic involvement, the use of chemoimmunotherapy and the age of most of our patients, it is essential to consider patients with AL amyloidosis as an extremely vulnerable population, with limited reserves to fight COVID-19. As we accumulate data, we will be able to provide better care to our patients, perhaps with more specific and safe therapies for the infection. All patients with systemic AL amyloidosis should be informed of their vulnerability and encouraged to adhere to measures to prevent infection. We should assure our patients with AL amyloidosis that we will continue our efforts to provide optimal care, even during this period of shortages and limited healthcare resources.

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Conflicts of interest

Efstathios Kastritis received honoraria for educational lectures and participated in advisory boards from Amgen, Genesis Pharma, Janssen, Takeda, and received research support from Janssen and Amgen. VS – Research funding to the institution: Celgene, Prothena, Takeda, Janssen, Scientific advisory board: Proclara, Caleum SOS – Research funding to the institution: Prothena, Janssen, Sanofi. Scientific advisory board: Caleum, Prothena, Janssen, Sanofi and Takeda. Honoraria for educational lectures from Janssen and Takeda. Travel grants from Janssen, Takeda and Medac. Ute Hegenbart has received travel grants from Janssen, Prothena and Pfizer, served on the advisory boards for Pfizer and Prothena, and has received honoraria from Janssen, Pfizer, Alnylam and Akcea. Joan Blade has received honoraria for lectures and advisory boards from Janssen, Celgene, Amgen, Takeda and Oncopeptides. Maria T. Cibeira received honoraria for educational lectures from Janssen, Celgene and Amgen, and

advisory boards from Janssen and Akcea. MR: research funding, travel fees and accommodation from Janssen. Meletios A. Dimopoulos received honoraria/personal fees from Amgen, BMS, Celgene, GSK, Janssen, Takeda. Stefan Schönland has received research funding from Janssen and Sanofi and travel grants from Janssen, Prothena, Takeda and Medac, served on the advisory boards for Janssen, Takeda and Prothena, and has received honoraria from Janssen, Takeda, Prothena. Monique Minnema, honoraria to institution Amgen, Janssen, Servier, Gilead. Takeda, BMS. Research funding to institution: Celgene, Travel grants Amgen, Celgene.

Author contributions

Efstathios Kastritisprepared the first draft, Ashutosh Wechalekar, Stefan Schönland, Vaishali Sanchorawala, Giampaolo Merlini, Giovanni Palladini, Monique Minnema, Murielle Roussel, Arnaud Jaccard, Ute Hegenbart, Shaji Kumar, Maria T. Cibeira, Joan Blade, Meletios A. Dimopoulos reviewed and made substantial changes and additions in the manuscript and provided their expert opinion.

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