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REVIEW

THE AMERICAN JOURNAL of MEDICINE®

COVID-19 and Light Chain Amyloidosis, Adding Insult to Injury

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ABSTRACT

Light chain (AL) amyloidosis is a potentially fatal disease of monoclonal plasma cells that leads to accumulation of light chain amyloid fibrils, organ damage, and the manifestations of clinical disease. Meanwhile, coronavirus disease 2019 (COVID-19) is a disease caused by infection with the severe acute respiratory syndrome coronavirus 2 virus, with the potential to cause severe systemic illness and death. There is significant overlap in the demographics and comorbidities observed in AL amyloidosis and those associated with highest risk for severe morbidity and mortality due to COVID-19. This overlap creates unique challenges in caring for patients with AL amyloidosis, which are further compounded by the immunosuppressive nature of anti-plasma cell therapies, the need for frequent clinical assessments, and the exclusion of AL amyloidosis patients from initial COVID-19 vaccine trials. Herein, we highlight many of the relevant concerns related to COVID-19 and the treatment of AL amyloidosis, summarize a general approach for AL amyloidosis management amidst the ongoing COVID-19 pandemic, and discuss current guidance about COVID-19 vaccination of patients with AL amyloidosis.
 • *The American Journal of Medicine (2022) 135:S49–S52*

KEYWORDS: AL amyloidosis; COVID-19; COVID vaccination; SARS-CoV-2

INTRODUCTION

Light chain (AL) amyloidosis is a rare disease with an incidence of ~3000-4000 cases/year in the United States, although many cases likely go undiagnosed.[1-4] The most common organ systems involved include the cardiovascular, renal, hepatic, gastrointestinal, and nervous systems, as well as other lymphatic and soft tissues.[5] The current AL amyloidosis treatment paradigm centers on lymphocyte/plasma cell-targeted therapies to suppress amyloid fibril production, as discussed in more detail elsewhere in this issue.[2]

Following early World Health Organization reports in December 2019 describing a "pneumonia" of unknown etiology emerging in Wuhan, China, coronavirus disease 2019 (COVID-19) has swept the globe, leading to >400 million cases and >5.7 million deaths worldwide, as well as >75 million cases and over 900,000 deaths in the United States.[6,7] While little was known about COVID-19 as the pandemic began, we now understand that COVID-19 is a systemic disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Striking overlap exists between the demographics and organ dysfunction associated with AL amyloidosis and severe COVID-19 infection. Here we discuss some of these factors while summarizing an evidence-based approach for AL amyloidosis management amidst the COVID-19 pandemic.

AGE

The incidence of AL amyloidosis increases with age, with a median age at diagnosis of 64 years, and <5% of patients diagnosed at <40 years of age.[8,9] Meanwhile, advanced age has been reported as a significant risk factor for severe COVID-19 and death.[10] According to Centers for Disease Control and Prevention data, those aged 50-74 years have a two-fold increased risk of acquiring COVID-19 (relative to ages 5-17 years) but a 25- to 35-fold increased risk of hospitalization and a 400- to 1100-fold increased risk of death due to COVID.[11] Therefore, the large majority of patients

Funding: None.

Conflicts of Interest: None.

Authorship: All authors had access to the data and contributed to writing the submitted manuscript.

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0002-9343/
https://doi.org/10.1016/j.amjmed.2022.01.005

with AL amyloidosis face notably increased risk of severe COVID-19 and death based on the age demographic alone.

SEX

Males account for ~65%-70% of AL amyloidosis cases, and male sex is an independent risk factor for severe COVID-19 infection as well as mortality.[10] One recent meta-analysis including >3 million cases from 44 countries found that men were more likely to develop severe COVID-19 requiring admission to an intensive care unit (odds ratio 2.84; 95% confidence interval, 2.06-3.92) and also significantly more likely to die from COVID-19 (odds ratio 1.39; 95% confidence interval, 1.31-1.47).[12] Notably, this same increased risk was seen in the prior SARS-CoV-1 and Middle East respiratory syndrome viral outbreaks as well. These may be attributable to differences in the innate antiviral responses and adaptive immunity toward viral antigens in females compared with males, leading to more effective viral control, reduced risk of severe disease, and decreased mortality due to COVID-19. Thus, the increased risk of severe COVID-19 in men represents a proportionally increased risk to AL amyloidosis patients, the majority of which are male.

CLINICAL SIGNIFICANCE

- Light chain (AL) amyloidosis is associated with significant organ dysfunction that increases risk of coronavirus disease 2019 (COVID-19) morbidity and mortality.
- Anti-plasma cell therapies for AL amyloidosis are immunosuppressive and further increase risk associated with COVID-19 infection.
- Therapy for symptomatic AL amyloidosis should not be unnecessarily delayed, and modifications to standard therapies should be evidence based, whenever possible.
- COVID-19 vaccination with a US Food and Drug Administration emergency use-authorized vaccine is strongly recommended, along with standard risk-mitigation measures.

COMORBIDITIES

AL amyloidosis is a systemic disease with deposition of amyloid fibrils leading to multisystem organ toxicity. The organs most commonly affected by AL amyloidosis include the cardiovascular (50%-70%), renal (50%-60%), hepatic (10%-30%), gastrointestinal (10%-20%), and nervous systems (20%-30%).[2,5,9] The presence of pre-existing organ dysfunction due to AL amyloidosis places such patients at markedly increased risk of severe COVID-19 infection, which has been documented to affect each of these organ systems.[13] This overlap in multisystem organ involvement between AL amyloidosis and COVID-19 has the effect of adding further insult to pre-existing injury for AL amyloidosis patients who contract SARS-CoV-2.

IMMUNOSUPPRESSIVE THERAPY

AL amyloidosis is characterized by a population of dysfunctional plasma cells, but can also be associated with an underlying hematologic malignancy of clonal B-cells (eg, non-Hodgkin's lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia) or of clonal plasma cells (eg, multiple myeloma, lymphoplasmacytic lymphoma). Therefore, patients with AL amyloidosis are at increased baseline risk of infection, including from SARS-CoV-2. In addition, most plasma cell-targeted therapies used for AL amyloidosis are inherently immunosuppressive and associated with increased risk of infection. A recent study found markedly prolonged shedding of live SARS-CoV-2 viral particles (>60 days) in patients who recently underwent hematopoietic cell transplantation (HCT), whereas the average period of viral shedding has been shown to be 10-15 days or less within the general population.[14,15]

Strategies to Optimize Treatment Efficacy While Mitigating Risk During the COVID-19 Pandemic

With the significant overlap between AL amyloidosis patient demographics and risk factors for severe COVID-19 and death, a comprehensive strategy is needed to mitigate risk from COVID-19 while providing standard-of-care AL amyloidosis therapy (**Table**[16]). This imperative is underscored by the observation that the risk of COVID-19 infection is frequently outweighed by the risk of amyloid-related death, with <6-month median survival for symptomatic AL amyloidosis patients with cardiac involvement (Cardiac Stage IIIb-IV).[2] Such a comprehensive strategy may focus on several domains, and the overarching concept is generally applicable to a variety of diseases where the demographics, disease sequelae, or disease treatments confer increased risk to COVID-19. Those domains include following universal precautions for COVID-19 risk reduction, increasing the use of telemedicine and technology-assisted clinical assessments to reduce in-person exposures, developing patient-specific evidence-based strategies to deliver optimal treatment while mitigating risk, and finally, developing standardized approaches to managing treatment in the event of an acute COVID-19 infection.[16]

For patients with AL amyloidosis, mask-wearing, maintaining physical distance, good hand hygiene, and vaccination represent high-yield universal precautions that should be employed to the fullest extent possible. Meanwhile, a multifaceted, deliberate, and individualized approach to patient care should balance the considerable risks associated with AL amyloidosis alongside the immunosuppressive nature of AL amyloidosis therapies, the ongoing risks of COVID-19, and the evolving nature of the COVID-19 pandemic.

Table Strategies to Mitigate Risk for AL Amyloidosis During the COVID-19 Pandemic

Universal Precautions
- Wear masks regularly
- Sanitize hands frequently, disinfect commonly used surfaces
- Maintain physical distancing, avoid crowds
- Avoid contact with those who are sick
- Get vaccinated against SARS-CoV-2

Telemedicine
- Obtain vital signs at home (HR, BP, temp, SpO_2, RR, weight)
- Use local labs for blood work, if feasible
- Defer specialized or in-person testing, if/when medically appropriate

Treatment Principles
- SOC induction therapy for newly diagnosed should not be delayed
- SOC salvage therapy for relapsed or refractory disease should not be delayed

Suggested Treatment Regimen Modifications
- Use SC bortezomib in place of IV bortezomib
- (Relapsed disease) Use PO ixazomib in place of bortezomib
- Use PO cyclophosphamide in place of IV cyclophosphamide
- Use SC daratumumab in place of IV daratumumab
- Dose reduce or eliminate steroids with lenalidomide monotherapy
- Consider early completion of therapy or reduced schedule in carefully selected patients (e.g. CR, preserved organ function)
- Consider delaying autologous stem cell transplantation in carefully selected patients

Management of COVID-19 infection
- Defer anti-plasma cell-directed therapies until after recovery from COVID-19
- In cases of severe COVID-19, steroids have shown a survival benefit and may be considered[16]

AL = light chain; auto-HCT = autologous hematopoietic cell transplantation; BP = blood pressure; COVID-19 = coronavirus disease 2019; CR = complete remission; Dx = diagnosis; HR = heart rate; IV = intravenous; PO = oral; RR = respiratory rate; SARS-CoV-2 = severe acute respiratory virus 2; SC = subcutaneous; SOC = standard of care; SpO_2 = pulse oximetry; Temp = temperature.

The proposed risk mitigation strategies should be applied on a case-by-case basis, taking into account patient preference and all relevant clinical factors.

AL AMYLOIDOSIS AND VACCINATION

There are currently 3 separate COVID-19 vaccinations that have attained US Food and Drug Administration (FDA) Emergency Use Authorization or Approval: the Pfizer-BioNTech COVID-19 vaccine (Pfizer Inc., New York, NY; BioNTech, Mainz, Germany), the Moderna COVID-19 vaccine (Moderna US, Cambridge, Mass), and the Janssen COVID-19 vaccine (Janssen Biotech Inc., Horsham, Pa).[17] However, it is important to note that the pivotal studies that led to these FDA authorizations excluded patients on active chemotherapy treatments, including AL amyloidosis patients. Therefore, the effectiveness of these vaccines in immunocompromised patients and those receiving active therapies for AL amyloidosis is unknown. Prior data found highly variable vaccine responses to influenza, pneumococci, varicella zoster and *Haemophilus influenzae* B in patients receiving treatment for hematologic malignancies, with seroconversion rates ranging from 20%-70%.[18] An observational retrospective cohort study of 261 cancer patients who contracted COVID-19 found similarly variable seroconversion rates of 33%-60% in patients receiving anti-CD20 therapy, chimeric antigen receptor T-cell therapy, and HCT.[19] These data suggest that seroconversion to COVID-19 vaccination among AL amyloidosis patients on active therapies may be significantly attenuated when compared with those subjects included in the trials leading to the vaccine authorizations.

Nevertheless, with the increasing availability of COVID-19 vaccines and the available safety data suggesting all 3 FDA emergency use authorized or approved vaccines are safe and well tolerated, the American Society of Hematology, the American Society for Transplantation and Cellular Therapy, and the International Myeloma Society have issued guidance in support of COVID-19 vaccination for patients with underlying hematologic malignancies, including AL amyloidosis, with whichever COVID-19 vaccine formulation is most readily available, unless contraindicated.[20,21] The timing of vaccination may be tailored to the patient's individual clinical situation, but in general should be performed as soon as is reasonable. Of note, vaccination should not delay the initiation of induction chemotherapy for patients with newly diagnosed and symptomatic AL amyloidosis. Patients who have recovered from a prior COVID-19 infection should still receive COVID-19 vaccination, as natural immunity to COVID-19 following infection is variable, can wane over time, and may not be protective to alternative COVID-19 variant strains.

When scheduling the COVID-19 vaccination, one should ideally target a goal absolute neutrophil count of >500/uL and platelets >50,000/uL to optimize the chances of vaccine response and minimize the risk of an intramuscular hematoma, respectively. For patients in a very good partial remission or complete remission for whom a brief treatment delay is not a concern, one may reasonably hold treatment 7 days prior to the first vaccine dose through 7 days after the second vaccine dose (~5-6 weeks), followed by any additional indicated vaccine doses at the appropriate interval without treatment interruption. If such a delay is not feasible, holding treatment 2-7 days prior to the first dose and waiting 10 days before restarting therapy (~2 weeks), while administering all subsequent doses at the appropriate interval without treatment interruption, may be reasonable. Patients receiving lenalidomide monotherapy may be able to continue treatment without interruption, given that the available data suggest that lenalidomide may either have no effect or may have a beneficial effect on vaccine responses.[22,23] Following auto-HCT, these authors recommend waiting a minimum of 3 months post-transplant to administer COVID-19 vaccination, based on data suggesting diminished vaccine responsiveness

in the months immediately post-HCT.[18] If a patient has been vaccinated prior to auto-HCT, data are not currently available regarding if or when to revaccinate post-HCT. Therefore, it may be reasonable to delay COVID-19 vaccination until after completion of auto-HCT if the timing of auto-HCT is imminent. Furthermore, there are no clinically validated tests to verify vaccine seroconversion among immunocompromised patients receiving COVID-19 vaccination.

CONCLUSION

Patients with AL amyloidosis carry a significantly increased risk of severe COVID-19 infection and death due to age, sex, comorbidities, and disease- and treatment-related immunosuppression. However, in most cases, the risk of morbidity and mortality from untreated AL amyloidosis exceeds that of COVID-19. Therefore, current guidance supports continued treatment for AL amyloidosis during the COVID-19 pandemic, with risk mitigation precautions including universal COVID-19 precautions (eg, mask-wearing, physical distancing), increased telemedicine care, and evidence-based adjustments to the treatment regimen. COVID-19 vaccination is generally recommended by major professional societies for all patients with AL amyloidosis, despite potential for lower seroconversion rates in patients with hematological malignancies undergoing active therapy.

CME STATEMENT

This article is published as part of a supplement supported by unrestricted educational grants from Alnylam Pharmaceuticals and Janssen Pharmaceuticals.

Credits Available for this Activity https://cme.wustl.edu/go/amyloidosis.

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References

1. Kyle RA. Amyloidosis: a convoluted story. *Br J Haematol* 2001;114 (3):529–38.
2. Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. *Blood* 2020;136(23):2620–7.
3. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. *Blood Adv* 2018;2(10):1046–53.
4. Kyle RA, Larson DR, Kurtin PJ, et al. Incidence of AL amyloidosis in Olmsted County, Minnesota, 1990 through 2015. *Mayo Clin Proc* 2019;94(3):465–71.
5. Merlini G, Dispenzieri A, Sanchorawala V, et al. Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers* 2018;4 (1):38.
6. World Health Organization. Novel coronavirus (2019-nCoV) situation report −1. January 21, 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf. Accessed April 4, 2021.
7. Johns Hopkins University & Medicine, Coronavirus Resource Center. COVID-19 Dashboard. Available at: https://coronavirus.jhu.edu/map.html. Accessed April 4, 2021.
8. Shimazaki C, Hata H, Iida S, et al. Nationwide survey of 741 patients with systemic amyloid light-chain amyloidosis in japan. *Intern Med* 2018;57(2):181–7.
9. Muchtar E, Gertz MA, Kyle RA, et al. A modern primer on light chain amyloidosis in 592 patients with mass spectrometry−verified typing. *Mayo Clin Proc* 2019;94(3):472–83.
10. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584 (7821):430–6.
11. Centers for Disease Control and Prevention. COVID-19 risks and vaccine information for older adults. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html. Accessed April 4, 2021.
12. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun* 2020;11(1):6317.
13. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020;26(7):1017–32.
14. Aydillo T, Gonzalez-Reiche AS, Aslam S, et al. Shedding of viable sars-cov-2 after immunosuppressive therapy for cancer. *N Engl J Med* 2020;383(26):2586–8.
15. Bullard J, Dust K, Funk D, et al. Predicting infectious severe acute respiratory syndrome coronavirus 2 from diagnostic samples. *Clin Infect Dis* 2020;71(10):2663–6.
16. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021;384(8):693–704.
17. US Food and Drug Administration (FDA). COVID-19 vaccines. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines. Accessed April 4, 2021.
18. Ludwig H, Boccadoro M, Moreau P, et al. Recommendations for vaccination in multiple myeloma: a consensus of the European Myeloma Network. *Leukemia* 2021;35(1):31–44.
19. Thakkar A, Pradhan K, Jindal S, et al. Patterns of seroconversion for SARS-CoV2-IgG in patients with malignant disease and association with anticancer therapy. *Nat Cancer* 2021;2(4):392–9.
20. International Myeloma Society. Recommendations for the management of myeloma patients during the COVID-19 pandemic. Available at: https://myeloma.wpengine.com/wp-content/uploads/2021/03/PM-COVID-vaccination-in-MM-guidelines-The-Final.pdf. Accessed April 4, 2021.
21. American Society of Hematology. General principles of COVID-19 vaccines for immunocompromised patients. Available at: https://www.hematology.org/covid-19/ash-astct-covid-19-and-vaccines. Accessed April 4, 2021.
22. Palazzo M, Shah GL, Copelan O, et al. Revaccination after autologous hematopoietic stem cell transplantation is safe and effective in patients with multiple myeloma receiving lenalidomide maintenance. *Biol Blood Marrow Transplant* 2018;24(4):871–6.
23. Noonan K, Rudraraju L, Ferguson A, et al. Lenalidomide-induced immunomodulation in multiple myeloma: impact on vaccines and antitumor responses. *Clin Cancer Res* 2012;18(5):1426–34.