Canadian Journal of Cardiology 38 (2022) 1144–1146

Editorial

Heart Transplantation for Cardiac Amyloidosis: The Need for High-Quality Data to Improve Patient Selection

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See article by Akintoye et al., pages 1263–1270 of this issue.

Recent years have witnessed tremendous advances in the management of patients with cardiac amyloidosis. Important developments include improved awareness of the disease and how to recognize it, better diagnostic techniques, and—perhaps most significantly—new and more effective therapies to improve outcomes.[1] Such advances have occurred for both amyloidosis disease subtypes that predominantly cause cardiac involvement; light-chain (AL) amyloidosis, a hematologic malignancy caused by clonal plasma cell proliferation, resulting in extracellular deposition of misfolded immunoglobulin light-chains, and transthyretin amyloidosis (ATTR), caused by misfolding of the hepatically derived transport protein transthyretin (TTR), resulting from either a mutation in the TTR gene (variant or hereditary ATTR [ATTRh]) or an age-related disorder occurring in the absence of a gene mutation (ATTR wild-type [ATTRwt]). A number of new therapies are now in various stages of development as well, raising hope that treatment options and outcomes will continue to improve for patients with a disease that was previously considered extremely rare and almost universally fatal. Such progress has led to both tremendous excitement and also recognition of the need for further research toward optimizing use of such therapies and related disease management approaches such as monitoring and surveillance for treatment response and progression of disease.[2]

In contrast with this rapidly evolving landscape is the fact that comparatively little progress has been made in recent years toward the care of those patients with the most advanced disease: namely, those with end-stage heart failure. Treatment options and approaches for these patients have changed little in the last decade. For example, although there have been limited reports describing success with left ventricular assist device therapy,[3] patients with cardiac amyloidosis are generally considered unsuitable candidates, largely because of their relatively small left ventricular cavity size and poor right ventricular systolic function, among other factors. This leaves heart transplantation as the only viable option for patients with cardiac amyloidosis and end-stage heart failure, although this is a complex and high-risk undertaking for which knowledge and care practices have evolved little in recent years. When considering the modern role of heart transplantation for patients with cardiac amyloidosis and advanced heart failure, there are a number of factors of which transplant programs need to be aware and mindful.

One important factor to consider when evaluating the suitability of a patient with cardiac amyloidosis for heart transplant is the difference between AL and ATTR disease subtypes. Although there are multiple similarities in cardiac phenotype and clinical manifestations between the 2—including extracardiac manifestations such as peripheral and autonomic neuropathy—it must be recognized that these are, in fact, different diseases with different clinical courses and treatment approaches. AL amyloidosis often has a rapidly progressive course. The kidneys are the most frequently affected organs, followed by the heart, with involvement of both organs being common. The efficacy of modern chemotherapy regimens (some of which contain classes of agents also used for immunosuppression following heart transplant) has improved significantly over the last decade, with newer agents currently under investigation as well. Autologous stem cell transplantation may be curative for eligible patients; however, the risks are often prohibitive for patients with advanced end-organ involvement. The strategy of heart transplantation as a bridge to stem cell transplant has been used successfully by select centres[4-6]; however, this approach is very complex and high risk with regard to patient selection and post-heart transplant care.[7] Conversely, ATTR is often slowly progressive, with the heart and nervous system being the most commonly affected organs (often both). Disease-modifying therapies have become available in the last few years: namely, TTR-stabilization (tafamidis) for patients with cardiomyopathy and suppression of TTR production (inotersen and patisiran) for ATTRh polyneuropathy. These agents are designed to attenuate progression of disease rather than

Received for publication April 25, 2022. Accepted May 16, 2022.

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See page 1146 for disclosure information.

https://doi.org/10.1016/j.cjca.2022.05.015

improve symptom burden (although in clinical trials a small number of patients demonstrated clinical improvement), with multiple new therapies currently in various stages of development. How the availability of these therapies will affect the need for heart transplantation in this patient population remains to be seen. It has been speculated that the use of liver transplantation, with or without concurrent or sequential heart transplantation for patients with heart failure, as a "curative" therapy for patients with ATTRh will decline with the availability of disease-modifying medical therapies; however, this, too, has yet to be confirmed. ATTRwt is the more common subtype in North America; however, the majority of these patients are above a suitable age range for heart-transplantation eligibility. Features that both AL and ATTR amyloidosis share with respect to a patient's heart transplantation eligibility are that this is often limited by extracardiac involvement, as both diseases are, in fact, systemic,[8] and, as a result of this and other factors, patients with cardiac amyloidosis are rarely eligible for heart transplantation.

In this issue of the *Canadian Journal of Cardiology*, Akintoye et al. provide an update on trends and outcomes in heart transplantation for cardiac amyloidosis patients from the United Network of Organ Sharing (UNOS) database,[9] which manages the national organ transplantation system in the United States. Other recent reports from either UNOS or individual transplant centres have suggested that although waitlist mortality remains higher than average,[10] patients with cardiac amyloidosis can experience outcomes similar to other patients without amyloidosis post-transplant when selected carefully,[5,11] suggesting an ongoing role for heart transplantation in this population. "Careful selection" has been variably described as limited extracardiac disease, and demonstration of responsiveness to chemotherapy for patients with AL amyloidosis. Akintoye et al. add to these recent publications by examining patterns of heart transplantation for cardiac amyloidosis patients from 2010 to 2019, stopping before the onset of the COVID-19 pandemic because of its impact on organ transplantation and the potential to skew the findings.

What did the authors find? Perhaps the most interesting result from their report is that even though heart transplantation for cardiac amyloidosis remains rare, the frequency has been steadily increasing over the past decade, increasing from only 22 heart transplants in 2010 to 59 in 2019.[9] It is not clear whether this trend is widespread across US transplant programs or being driven by a smaller number of referral centres, although the latter is suspected. This trend most likely reflects overall improvements in cardiac amyloidosis care over the last decade, especially with regard to the use of disease-modifying therapies, as more patients with heart failure survive to be considered for heart transplantation. Another finding is that waitlist mortality remains high compared with that of patients without amyloidosis, demonstrating that despite improvements in amyloidosis therapies, this remains a high-risk population. However, it is possible that recent changes to the US adult heart allocation policies, which helps prioritize patients with restrictive cardiomyopathy such as cardiac amyloidosis, may also address this need.[12] Finally, graft survival rates were significantly lower for patients with cardiac amyloidosis receiving heart transplant compared with those with dilated cardiomyopathy, although they were higher compared with patients categorized as having restrictive cardiomyopathy not caused by amyloidosis.

Other findings from Akintoye et al. are more difficult to put into context with respect to clinical implications, as a result of the inability to characterize amyloidosis subtype in the UNOS database. This is particularly true for the analysis performed by the authors to determine risk factors for graft failure among heart transplant recipients with cardiac amyloidosis. Their analysis demonstrated that the presence of renal failure requiring dialysis at the time of heart transplant listing and a history of malignancy (not caused by multiple myeloma or other plasma cell dyscrasias) were the factors most significantly associated with graft failure post-transplant. This leaves one wondering what the amyloidosis subtype composition of the 330 transplant recipients included in this cohort was and whether these risk factors apply similarly to patients with AL vs ATTR amyloidosis. It is likely these findings are driven by patients with AL amyloidosis, as end-stage renal dysfunction is not common among patients with ATTR amyloidosis nor is heightened susceptibility to solid organ malignancy; however, in the absence of data, this can only be speculated, and the clinical significance is unclear.

There are many other potential limitations of using the UNOS database for the proposed analysis. In addition to lacking information regarding disease subtype, information regarding the extent of neurologic involvement or other extracardiac manifestations is not available and potentially important in predicting outcomes before or after transplant.[13] As with any administrative database, there can be inaccuracies in data entry and missing values. However, the authors used multiple imputation, which is an effective way to handle missing values.[14] The authors also excluded patients undergoing multiorgan transplant, not capturing patients cardiac amyloidosis patients referred for heart-liver (for example in patients with ATTRh) or heart-kidney transplants.[15,16] Strategies for donor and recipient selection continue to evolve,[17] and the current analysis is not powered to determine whether these changes have affected outcomes for patients with cardiac amyloidosis. Finally, the cohort was limited to a more contemporary population to evaluate the impact of modern cardiac amyloidosis care, but this limits the sample size available even in a database as large as UNOS. This limitation is evidenced by residual differences in the matched populations of patients with cardiac amyloidosis and non-amyloid restrictive cardiomyopathies. With all these considerations, it is unclear if the UNOS database is well suited to study rare diseases that have specific characterizing variables of interest.

What is clear is that if selection criteria for—and outcomes after—heart transplantation for patients with cardiac amyloidosis are going to improve, further research is needed, using information sources that can provide data specific to this complex and unique patient population, while also combining data from multiple centres to improve statistical power for this rare disease. Despite the recent advances in the field of cardiac amyloidosis, these barriers remain a challenge not only for research related to heart transplantation but for other aspects of disease management as well. This limitation in part has fueled growing interest in dedicated amyloidosis patient registries as a potential approach to addressing such knowledge gaps.[18] In the meantime, heart transplant programs will

continue to use a combination of clinical experience and existing principles of heart transplant recipient selection and post-transplant care to guide management for patients with cardiac amyloidosis and end-stage heart failure. For these reasons, it is likely that heart transplantation for patients with cardiac amyloidosis will remain concentrated in centres with high transplant volumes and dedicated expertise in amyloidosis care. Despite the limitations imposed by the UNOS database, the contribution of Akintoye et al. is important,[9] both for the insights it provides and for how it highlights the deficiencies of the currently available data sources in this area and the need for improved information gathering.

Funding Sources

No funding was provided for this article.

Disclosures

Dr Fine has received research funding support and consulting and speaking honoraria from Pfizer, Alnylam, Ionis, Sobi, and Eidos. Dr Miller received research support and consulting honoraria from Pfizer.

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