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Host-directed therapies for tuberculous pericarditis

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ABSTRACT

TB Pericarditis is associated with significant inflammatory and immune responses which can paradoxically cause injury to the pericardium and myocardium. Management with anti-TB therapy alone does not prevent complications or reduce mortality. Thus the prevailing view is that adjunct host-directed therapies such as use of glucocorticoid treatment could attenuate destructive inflammatory responses and improve morbidity and mortality rates. A recent trial showed no advantage of using adjunct corticosteroid treatment on the combined endpoint of death, cardiac tamponade or constriction. The current lack of effective medical treatment for reducing the significant morbidity and mortality associated with TB pericarditis, highlights the urgent need for newer approaches to treating the disease. Newer treatment options for pericarditis using adjunct host-directed therapies, including autologous bone-marrow-derived Mesenchymal Stromal Cells (MSCs) therapy, now require evaluation in randomized placebo-controlled controlled trials.

Cardiac diseases are very common causes of inpatient admission to hospitals and impose a large burden on health services worldwide.[1,2] Pericarditis, inflammation of the membranous pericardial sac surrounding the heart, is a common cause of pericardial effusion, cardiac tamponade, cardiac failure and constrictive pericarditis in sub-Saharan Africa (SSA).[3] Whilst infectious pathogens are more common causes of pericarditis there are other non-communicable diseases that result in pericardial disease such as cancer, autoimmune diseases, connective tissue disorders, endocrine, myopericardial diseases and pericardial injury syndromes.[4–8] The relative frequency of different underlying causes of pericarditis depends on the local epidemiology, the hospital setting and management protocols in place. Thus the diagnostic and management algorithms for pericarditis are dependent on the background prevalence of the underlying aetiology. Many cases still remain idiopathic in developed countries, whereas tuberculosis, HIV infection and associated opportunistic infections are important causes in high TB and HIV endemic countries.[6,9,10]

A spectrum of bacterial and viral pathogens cause pericarditis, although it is assumed in sub-Saharan Africa (SSA) that the majority of cases of pericarditis are due to tuberculosis (TB), some of whom often have concomitant human immunodeficiency virus (HIV) infection.[5,9] The treatment of pericardial diseases in SSA is largely empirical because of the relative lack of randomized trials compared with other cardiovascular diseases.[7,11] The main clinical forms of pericardial diseases in SSA are subacute pericardial effusion, effusive constrictive and constrictive pericarditis.[8,12] Despite empiric anti-TB therapy, pericardial drainage, or pericardiectomy, mortality rates are high (up to 26% at 6 months but is even higher (40%) among people living with HIV infection).[5,7,9]

Pericarditis from any cause is associated with significant inflammatory and immune responses which can paradoxically cause injury to the pericardium and myocardium. Management with antimicrobial therapy alone does not prevent complications or reduce mortality. Thus the prevailing view is that adjunct host-directed therapies such as use of glucocorticoid treatment could attenuate destructive inflammatory responses and improve morbidity and mortality rates.[3,6,7] Current guidelines[9,10] recommend treatment with glucocorticoids in addition to anti-TB drugs in patients with TB pericarditis although the evidence base on which this recommendation was developed remains weak.[13]

The results of a large placebo-controlled randomized clinical trial of two host-directed therapies in patients in Africa with presumed tuberculous pericarditis were published recently.[14] The IMPI (Investigation of the Management of Pericarditis) trial, was a multicenter, factorial-design trial that randomly assigned 1400 patients with pericarditis (two thirds were HIV-infected)

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to receive a course of high-dose prednisolone tapered over the course of 6 weeks or placebo. They were further randomized to receive placebo or five injections of heat-killed *Mycobacterium indicus pranii (M.w)*, an environmental saprophytic mycobacterium with assumed immunomodulatory effects.[15] The study results were clear - therapy with either intervention had no significant effect on the primary composite efficacy outcome of death, cardiac tamponade requiring pericardiocentesis, or development of constrictive pericarditis, and 18% of patients died. Both interventions increased the incidence of cancer among trial participants. There was an overall reduction in the development of constrictive pericarditis and in hospitalizations with prednisolone treatment regardless of HIV status. Thus, it has been suggested that patients who might benefit from immunomodulatory treatment may include those with large effusions, those with high levels of inflammatory cells in pericardial fluid, or those with signs of early constriction.[16] In addition, the study also confirmed the long-standing clinical observation that identification of the specific microbial etiology of pericarditis when patient presents at point of care with pericarditis is difficult, since only a quarter of patients in the study had microbiological confirmation.

A range of innate, adaptive and autoimmune immune responses are triggered in pericarditis, resulting in acute, sub-acute or chronic inflammation of the pericardium and cardiac tissue.[5–12] The cellular and cytokine responses contribute to pericardial and myocardial cardiac pathologies which subsequently compromise cardiac function.[7,8,11] Recent advances have focused attention on host-directed treatment options and provide renewed hope for better outcomes for infectious diseases associated with excess and aberrant destructive inflammation.[17–20] Augmentation or dampening of pro-inflammatory responses could be of value in the treatment of individuals who exhibit inflammation-induced tissue damage. It may also help revert an unsuccessful immune response back to a productive response and could induce long-lasting immune memory capable of providing continuous protection. This concept is being explored for treatment of cardiac conditions and immune based cytokine or cellular treatments are now being trialed for improving treatment outcomes of drug-resistant TB.[21–24]

Adjunct therapy using the patient's own bone marrow derived mesenchymal stromal cells (MSCs) may present a viable option for treatment of drug resistant TB since they modulate immune responses with beneficial trophic activity on damaged tissues.[17–24] The anti-scarring, and angiogenesis effects of MSCs may improve management outcomes in both immunocompromised and immunocompetent individuals. The infusion of autologous bone marrow derived MSCs have been found to be safe and to restore functional cellular immune responses in a phase 1 trial in Belarus patients with MDR-TB.[25] Host-directed therapies for cytomegalovirus and Epstein-Barr virus infections, have successfully used genome-scale gene expression profiles and drug-induced re-activation of latent viral pathogens to determine the optimal timepoints for immune interventions[26]

Similar strategies may be used to determine the best timepoint to offer adjunct therapies for patients with TB pericarditis. The current lack of effective medical treatment for reducing the significant morbidity and mortality associated with TB pericarditis, highlights the urgent need for newer approaches to treating the disease. Newer treatment options for pericarditis, such as cytokine therapies, the use of re-purposed drugs, or cellular therapy, including the use of autologous bone-marrow-derived MSCs requires now evaluation in randomized placebo-controlled controlled trials.

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