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An improved protocol for the treatment of fulminant myocarditis

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Fulminant myocarditis is a rare form of severe myocarditis that is most commonly caused by viral infection. Fulminant myocarditis is often pathophysiologically indistinguishable from milder forms of acute myocarditis but is categorically defined based on clinical disease progression. Patients may initially present with mild symptoms, such as fever, shortness of breath or heart palpitations, but rapidly progress to severe respiratory distress, arrhythmias, and cardiogenic shock. Fulminant myocarditis is more common among young, healthy adults and children but can afflict individuals of any age or gender. Patients who survive the acute phase of fulminant myocarditis have a good prognosis for long term survival; however, even with aggressive support, in-hospital mortality is approximately 50% (Caldeira et al., 2015; McCarthy et al., 2000; Robinson et al., 2015). Despite widespread access to supportive medications and ventricular assist devices which can ameliorate some signs and symptoms, few advances have significantly reduced fulminant myocarditis mortality in recent years.

Viral infection, which is the root cause of most fulminant myocarditis, can cause direct damage to myocardium, which results in the release of cytokines and cellular debris that induce a robust host inflammatory response. Cytokines recruit inflammatory cells, including leukocytes, monocytes and neutrophils, which infiltrate the myocardium to fight the viral infection. Ultimately, it may be the intense host immune response that is most devastating to patients; myocardial edema, apoptosis and necrosis of heart tissue can result. Heart failure, tachycardia and hypotension ensue, and the immune response may spread to other organs and cause liver and kidney failure along with severe respiratory distress. Conventional treatment largely represents a mosaic of interventions that are targeted to specific signs and symptoms and administered in stepwise manner as the disease progresses.

Frustrated with the poor efficacy of current treatment approaches to this devastating condition, Dr. Dao Wen Wang and co-workers developed a combined treatment approach and conducted a multi-center clinical trial (Li et al., 2019) that formed the basis for the recent expert consensus statement on fulminant myocarditis (Wang et al., 2019). The treatment regimen, called the Life Support-Based Comprehensive Treatment Regimen (LSBCTR) consisted of simultaneous mechanical support for the patient's heart and lungs in addition to medical treatments designed fight the viral infection and limit the host immune response to the infection. Mechanical support for the heart included intra-aortic balloon pump (IABP) to increase effective cardiac output and maintain blood pressure. If IABP failed to correct the failing heart, extra-corporeal membrane oxygenation (ECMO) was added. In addition, all fulminant myocarditis subjects received immediate mechanical ventilation support and hemodiafiltration or renal replacement therapies. Subjects were given neuraminidase inhibitors which prevented a critical step in viral replication, as well as glucocorticoids and intravenous immunoglobulins (IVIG) which dampened the host immune response. Of the 169 patients in this study, 41 of the 88 patients given standard care died in-hospital

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(46.6% mortality), while there were only 3 deaths among the 81 patients given the LSBCTR therapy (3.7% mortality).

The reduction in in-hospital mortality from fulminant myocarditis using this comprehensive treatment regimen is striking. A major key to the success of this new protocol was the aggressive use of combined therapy. Prior trials have examined the use hemodynamic support plus glucocorticoids or IVIG but found only modest clinical benefits (Caldeira et al., 2015; Robinson et al., 2015). The authors postulated that the primary problem in fulminant myocarditis is the host 'cytokine storm' and the extensive cellular infiltration of heart tissue by the patient's own immune system. Compared to previous studies, the combination of glucocorticoids and IVIG may limit this excessive immune response better than either treatment alone. A notable risk of dampening immune function is that it may also limit viral clearance and resolution of the viral infection; thus, the authors also used antiviral treatments (neuraminidase inhibitors) in their combined regimen. By attacking the disease process on multiple fronts, using aggressive hemodynamic support, immunosuppressive treatments, and antiviral medications, this new protocol dramatically improved outcomes for patients with fulminant myocarditis.

Despite the enormous success of this clinical trial, there are several notable limitations of the study. First, this study was not a randomized, prospective clinical trial; the new protocol was performed on all newly admitted patients and these subjects were compared to disease-matched historical controls. While likely a small effect, it is possible that incremental advances in hospital infrastructure and/or life support technologies played some role in improved patient outcomes. Second, the trial does not determine which of the multiple LSBCTR treatments are most critical to patient survival. Previous studies have not rigorously evaluated the combined use of glucocorticoids with IVIG or the addition of neuraminidase inhibitors for treatment of fulminant myocarditis. Despite these limitations, the authors put forth an improved protocol which others can refine and test in controlled trials to better understand the relative importance and optimal timing for each treatment component.

In conclusion, the study by Li, et al is pioneering work that describes an improved protocol which represents a significant step forward in the treatment of fulminant myocarditis. This protocol does not require deployment of novel technologies or medications; it is merely vigorous and immediate application of currently available treatments. The outcome also advances our understanding of the pathophysiology of fulminant myocarditis by highlighting the importance of body's overwhelming immune response and describing a mechanism to control it. Most importantly, implementation of this protocol for treatment of fulminant myocarditis has the potential to save the lives of many young, otherwise healthy individuals, who are likely to have excellent long-term prognoses.

Compliance and ethics *The author(s) declare that they have no conflict of interest. Clinical Trial Registration URL: http://www.clinicaltrials.gov. Unique identifier: NCT03268642.*

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