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Antimicrobial agents for myocarditis: target the pathway, not the pathogen

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Myocarditis is a serious and potentially life-threatening disorder that may lead to acute and/or chronic dilated cardiomyopathy and heart failure. Viruses are the most common pathogens associated with myocarditis and may cause cardiac injury by direct damage or through the immune and autoimmune reaction that follows viral infection. Antiviral agents, including pleconaril and interferon beta, have been used to treat acute and chronic viral myocarditis in small case series. Most therapeutic strategies that have targeted postviral and autoimmune inflammation have sought to inhibit adaptive immune components, including anti-heart antibodies and T lymphocytes, in the setting of lymphocytic or giant cell myocarditis.

Rarely, bacteria may cause acute myocarditis. Fournier *et al*[1] described eight patients with acute Q fever (*Coxiella burnetii*) who developed myocarditis. All eight patients were treated with doxycycline for a minimum of 14 days. Five patients fully recovered, two died and one was listed for heart transplantation. Vogiatzis *et al*[2] reported a 30-year-old man with *Coxiella burnetii* who presented with chest pain, ECG changes and elevated serum cardiac biomarkers. He remained symptom free for at least 2 years after 21 days of doxycycline. Murcia *et al*[3] reported a similar case of a 40-year-old man with *Coxiella burnetii* who presented with fever and rapidly developed symptoms of heart failure. The patient was treated with clarithromycin, as well as losartan and furosemide, and his cardiac function completely normalised by 6 months.

Myocarditis from *Chlamydia* and *Mycoplasma pneumoniae* may also respond to macrolide antibiotics. Hoefer *et al*[4] and Walder *et al*[5] reported a young woman with *Chlamydia pneumoniae* myocarditis who presented in acute heart failure. Apical core obtained during biventricular assist device (BiVAD) implantation showed massive diffuse lymphocyte infiltration and myocyte necrosis. Polymerase chain reaction and Southern blot analysis performed on a myocardial biopsy specimen detected *C pneumoniae* and parvovirus B19 genomes. Her cardiac function normalised and her BiVAD was explanted after treatment with ceftriaxone and erythromycin. Paz and Potasman[6] reported the response of five cases of *Mycoplasma pneumonia* myocarditis to antimicrobial treatment. Four were treated with

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erythromycin and one was treated with doxycycline. Four of the five patients experienced complete recovery, including normalisation of cardiac structure and function.

Macrolide antibiotics may also have a role in the treatment of non-bacterial myocarditis, which is much more common, but their effectiveness may be mediated through inhibition of matrix metalloproteinases (MMPs) rather than through a pathogen-specific mechanism. MMPs are involved in the degradation of extracellular matrix proteins which, in turn, leads to tissue remodelling. Several MMPs are elevated in experimental autoimmune myocarditis (EAM).[7] In the heart, MMPs have a significant role in the development of myocardial remodelling and subsequent heart failure. Tissue inhibitors of matrix metalloproteinases (TIMPs) play a key part in the regulation of MMP expression and activity.[8] Various cytokines, including interleukin 17, have been shown to alter the myocardial TIMP/MMP balance, resulting in increased MMP activity[9,10] that eventually leads to ventricular dilatation and cardiac dysfunction.

Specific TIMPs and MMPs differ in their effects on the myocardium in rodent myocarditis models. TIMP-1 expression increases in the myocardium after coxsackievirus B3 (CVB3)-mediated myocarditis. TIMP-1 knockout mice exhibit a profound attenuation of myocarditis with increased survival.[11] CVB3 infection of mice with EAM increases expression of MMP-2, MMP-9 and MMP-12 and activity of MMP-2 and MMP-9. In this model, TIMP-3 and TIMP-4 expression was downregulated, while TIMP-1 and TIMP-2 expression remained constant.[12] A subsequent study of CVB3-induced myocarditis in MMP-8 and MMP-9 knockout mice demonstrated that the infected MMP-9 knockout mice had greater myocardial injury and foci of infection than wild-type mice, while MMP-8 knockout mice had the same degree of myocardial injury, fibrosis and viral infection as wild-type mice.[13] These data suggest that MMP-9 may be protective in acute CVB3-induced myocarditis. Another study performed in transgenic mice demonstrated that MMP-2 has a cardioprotective role, reducing myocardial inflammation and dysfunction in tumour necrosis factor **α**-induced cardiomyopathy in mice.[14] The myocardial MMP/TIMP profile has an important role in the cardiac remodelling that frequently occurs in patients with acute myocarditis and may offer a novel target for therapeutic intervention.

In this issue of *Heart*, Hishikari and colleagues[15] report a trial of clarithromycin (CAM) for the treatment of EAM (***see page 523***). Six rats were treated from day 7 to day 21 with CAM, while six untreated rats served as controls. All 12 animals underwent induction of EAM at day 0. Vital signs and echocardiography were obtained at days 0, 14 and 21. At day 21, hearts were examined using histological and immunohistological stains and film in situ zymography.

Rats treated with CAM had significantly better outcomes than the non-treated rats. CAM treatment lessened the reduction of myocarditis-induced mean blood pressure, improved left ventricular systolic function, lowered heart/body weight ratio and reduced the extent of myocarditis. The number of myocardial CD4, CD8 and ED-1 positive cells and expression of MMP-2 and MMP-3 was decreased, as was MMP activity.

The Hishikari study demonstrates that CAM inhibition of MMP activity can prevent acute, autoimmune myocarditis. These in vivo results confirm previous in vitro findings that treatment with macrolide antibiotics alters immunological factors and suppresses MMP production and activity, leading to attenuation of the inflammatory response. These findings raise the possibility that CAM, which is effective in the rare patient with bacteria-induced acute myocarditis, might also be effective in the larger population of patients with idiopathic or, possibly, postviral myocarditis.

Several study features limit the applicability of Hishikari's findings to human myocarditis. Treatment with CAM began 7 days before induction of EAM. It is not possible to treat patients before the onset of acute myocarditis. Preclinical studies would need to demonstrate efficacy when animals were treated after the onset of disease. The data from studies of CVB-induced myocarditis suggest that MMPs may sometime help healing and limit myocardial damage. Hishikari's findings should be replicated in models of acute viral myocarditis before human studies, where viral aetiology is common, are considered. Perhaps most importantly, the CAM dose used in this study was 100 mg/kg/day. The equivalent dose in a 70 kg person would be 7000 mg/day, which is seven times the upper limit of the current recommended daily dosage for adults. Treatment at equivalent doses in patients would risk significant adverse effects, including QT prolongation, ventricular arrhythmias and gastrointestinal symptoms. The optimal dose in rodent models is not known and may be lower than that used in this study.

Despite these limitations, Hishikari's findings are provocative and deserve further investigation. If additional preclinical studies support the benefits of CAM at a dose and timing that could be used in clinical studies, the first clinical setting for CAM treatment might be in patients with chronic inflammatory cardiomyopathy and no viral genomes detected on endomyocardial biopsy. These patients are uncommon, but often progress to heart transplantation or death despite optimal clinical care. In this setting, the magnitude of potential benefit might be at least equal to the risk of CAM treatment.

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