Clinical and Molecular Aspects of Cardiomyopathies

Emerging Therapies and Clinical Trials

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KEYWORDS

• Rare cardiac diseases • New therapies • Precision medicine • Genetics • Cardiomyopathies • Clinical trials

KEY POINTS

- Cardiomyopathies are diseases of the myocardium, often genetically determined, associated with heterogeneous phenotypes and clinical manifestations.
- Despite significant progress in the understanding of these conditions, available treatments mostly target late complications, while approaches that promise to interfere with the primary mechanisms and natural history are just beginning to surface.
- The present review focuses on novel pharmacologic approaches to genetic cardiomyopathies, with a view to future developments and potential clinical implications.

Cardiomyopathies are diseases of the myocardium associated with heterogeneous morphofunctional phenotypes and clinical manifestations, frequently due to a genetic cause.[1] The last 2 decades have witnessed significant progress in the treatment of patients with cardiomyopathies, resulting in decreasing rates of mortality and morbidity.[2] However, available treatments largely target downstream complications, whereas approaches that promise to truly interfere with primary molecular mechanisms and change the natural history of myocardial disease are just beginning to surface.[3] Tailored pharmacologic therapies for cardiomyopathies remain an unmet need and a research priority.[4] In recent years, the establishment of centers of excellence and large international registries has allowed the recruitment of sizable patient cohorts,[5] whereas advances in cardiac imaging and genetic testing, deeper understanding of the molecular targets, and growing involvement by the pharmaceutical industry have led to a rapid increase in the number of dedicated trials (**Fig. 1**, **Table 1**). Nevertheless, formidable challenges remain: even the most prevalent cardiomyopathies are relatively uncommon compared with "classic" cardiac diseases, and others are undeniably rare. Furthermore, clinical presentation and outcome are heterogeneous;

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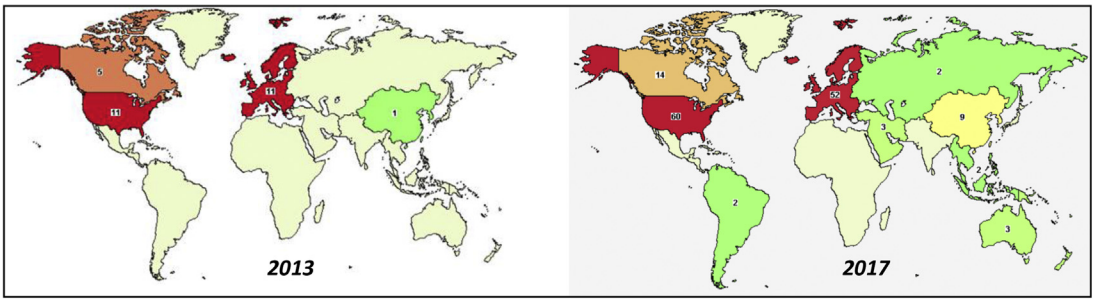

Fig. 1. Number of HCM registered trials across the world in 2013 and 2017. (*From* https://clinicaltrials.gov/ct2/results/map?term=hypertrophic+cardiomyopathy&map=.)

"hard" event rates are low, and resources are limited.[6] Most existing trials have targeted only specific subsets of patients and have necessarily used surrogate endpoints such as indexes of functional capacity or changes in left ventricular (LV) mass, fibrosis, and outflow gradients.[5] None was ever powered to assess the impact of therapeutic interventions on clinical course and outcome. Thus, even potentially effective drugs might fail to show their benefit due to inadequate endpoints, sample size, and time span of clinical experimentation. Consequently, the need for novel, specific trial design is emerging for these slowly progressive, chronic conditions largely affecting young individuals.[7]

The present review focuses on novel pharmacologic approaches to genetic cardiomyopathies, with a view to future developments and potential clinical implications. There are different levels of interventions that are being pursued, ranging from the most accessible, but less satisfactory, relief of symptoms, to more ambitious but still embryonic approaches attempting to prevent or reverse disease phenotypes (**Fig. 2**). Because it is not feasible to address the multitude of conditions in which research is ongoing, the authors have limited their focus to the principal paradigms, in order to illustrate the state of the art in the field.

EMERGING STRATEGIES FOR HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a common genetic disorder characterized by cardiac hypertrophy not explained by abnormal loading conditions, largely caused by genes coding for proteins of the sarcomere.[8] HCM has a 1:500 prevalence in the general population and represents a frequent cause of sudden cardiac death in the young, although the absolute incidence of events is rare.[2] Pharmacologic therapy plays a very important role in restoring quality of life and reducing risk of complications. Plausible options under investigation include the repurposing of well-known drugs, such as diltiazem or ranolazine, as well as development of novel agents targeting disease-specific abnormalities.[9] At the clinical level, current pharmacologic research focuses on 2 different approaches: modifiers of overt clinical HCM phenotypes and prevention of phenotype development in genotype positive "healthy" individuals.

Overt Hypertrophic Cardiomyopathy

One of the most intriguing hypotheses explaining HCM pathogenesis focuses on excess sarcomere activation and energy expenditure as the primary defect in HCM. Sarcomere mutations causing HCM are generally gain of function, producing overactivation of the contractile apparatus and profound metabolic changes ultimately leading to energy depletion and triggering of fibrosis.[10] A small-molecule allosteric myosin inhibitor, mavacamten (MYK-461; Myokardia, San Francisco, CA, USA), has recently been developed to restore physiologic contractile and energetic balance in HCM hearts by decreasing adenosine triphosphatase activity of the cardiac myosin heavy chain.[11] In an HCM mouse model, mavacamten effectively prevented development of LVH, myocyte disarray, and fibrosis and downregulated both hypertrophic and profibrotic gene expression[11] (**Fig. 3**). Phenotype reversal was observed in early stages, but not in older mice.[11] Human studies are now underway, and a phase 2 study has recently been completed to evaluate the efficacy, safety, and tolerability of mavacamten in subjects with symptomatic HCM and left ventricular outflow tract (LVOT) obstruction (NCT02842242); a large phase 2/3 study is due to start in 2018.

A previous attempt to reduce the energetic cost of the HCM myocardium and improve its efficiency was performed with perhexiline, a metabolic modulator that inhibits free fatty acid metabolism and enhances carbohydrate utilization by