Rajaie Cardiomyopathy and Myocarditis Registry: Protocol for an Observational Study

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Abstract- Most of the information on the natural history and management of cardiomyopathies and myocarditis in Iran has been obtained from cohort studies in a small number of patients. The prevalence of patients with cardiomyopathies referred to Rajaei Cardiovascular medical and research centers from all over the country is remarkable. Rajaie Cardiomyopathy and myocarditis Registry (RCMR) study is an observational registry of patients with four subtype of cardiomyopathy include: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM) as well as myocarditis designed to determine clinical characteristics, natural history, current therapeutic approaches, response to treatment and long-term outcomes of patients with cardiomyopathy and myocarditis. Prediction of mortality and response to different treatments in these patients using artificial intelligence is another aim of this Registry. COVID 19 Myocarditis and its sequence as cardiomyopathy seem a new challenge in forthcoming years. At the baseline visit, past medical history, clinical signs/symptoms, risk factors, physical examination and family history of cardiomyopathy, current standards for diagnostic workup and clinical follow-up, and relevant electrocardiogram echocardiography, cardiac magnetic resonance, Holter monitoring, or biomarker analyses will be checked. The outcome and results of various therapeutic approaches currently employed for patients, including implantable cardioverter defibrillator, cardiac resynchronization therapy, septal myomectomy, ablation, cardiac transplantation, and medications, will be assessed. Long-term outcomes, including the benefits and complications of therapeutic interventions, will be collected. A follow-up visit will be scheduled after 12 months for all patients, and survival status, hospitalizations, co-morbidities, medications will be assessed.

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Introduction

Cardiomyopathies are diverse groups of myocardial disorders associated with cardiac dysfunction that are not explained by coronary artery disease or abnormal blood circulation, leading to sudden death due to arrhythmia, progressive heart failure, or stroke (1,2). Myocarditis is known as any augmented immune response of the myocardium or inflammatory process diagnosed by histological and immunohistochemically findings and clinical presentations (3).

A significant health burden of all types of

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cardiomyopathies and myocarditis and their natural history in Europe and the USA are discussed in several studies and registries. The EURObservational Research Program (EORP) Cardiomyopathy registry was conceived by the European Society of Cardiology (ESC), and the Sarcomeric Human Cardiomyopathy Registry (ShaRe) are two examples of successful large multinational Registry in cardiomyopathy across Europe and USA (1,4).

Despite the relatively high prevalence of cardiomyopathy and myocarditis in Iran, the presentation and natural history of these disorders in Iranian population are not well defined and there is little data to describe the contemporary characteristics and practical management of patients in Iran. Rajaie cardiovascular medical and research center is a well-equipped and advanced tertiary specialized cardiovascular center where patients from all over the country are referred. Due to the remarkable number of referral patients with cardiomyopathy to this center, Rajaie Cardiomyopathy and myocarditis Registry (RCMR) was conceived to determine clinical characteristics, natural history, current therapeutic approaches, response to treatment and long-term outcomes of patients with cardiomyopathy and myocarditis. RCMR is an observational registry of consecutive patients with four cardiomyopathy subtypes: HCM, DCM, ARVC, RCM as well as myocarditis in adults and pediatrics. Prediction of mortality and response to different treatments in these patients using artificial intelligence is another aim of this Registry.

Study objectives

The objectives of the study are

- To determine natural history data on a wide spectrum of cardiomyopathy patients, cardiomyopathy mutation carriers and individuals who are part of a cardiomyopathy family.
- To determine demographic, genetic, and clinical characteristics of patients with cardiomyopathy and myocarditis and their families if necessary.
- To determine the characteristics of current standards for diagnostic modalities of patients with cardiomyopathy and myocarditis.
- To determine current therapeutic approaches and response to treatment in patients with various forms of cardiomyopathy and myocarditis.
- To determine long-term outcomes of cardiomyopathy and myocarditis.
- To predict mortality rate and response to different treatments in cardiomyopathy and myocarditis patients using artificial intelligence.
- To plan for future research studies (observational and interventional trials aimed at better symptom control or slowing down or delaying the onset and progression of cardiomyopathies).

Materials and Methods

Study design

The study is a registered single-center, observational study (NCT04304118) conducted in Rajaie cardiovascular medical and research center, enrolling consecutive patients with cardiomyopathy and myocarditis. The study received ethical approval from the local Ethics Committee on January 25, 2020 (IR.RHC.REC.1398.078), and the study is sponsored by the Rajaie cardiovascular medical and research center.

RCMR Consists of two phases: A pilot phase of the Registry restricted to adult patients with HCM for troubleshooting the process and validating the data set's structure and quality that will take six months. A Long-Term phase will be conducted to enroll all cardiomyopathy types in adults and children older than one year and enrollment of patients with clinically suspected or biopsy-proven myocarditis. This Phase will take five years to recruit eligible patients that all patients will have a one-year follow-up.

The executive committee and core laboratories

The principal investigators of the study are Freidoun Noohi, MD, Head of Rajaie cardiovascular medical and research center, and Majid Maleki, MD, Vice chancellor for research, Rajaie cardiovascular medical and research center. The executive committee will provide scientific leadership for conduct of RCM and the steering committee of Registry is responsible for overseeing the monitoring and data quality control procedures. They are responsible for the execution of monitoring according to the principles of Good Clinical Practice (GCP) and for supplying trained personal for this purpose

Participants

Participants will either have signs and symptoms of cardiomyopathies or myocarditis, be a member of cardiomyopathy family or are known to carry the cardiomyopathy mutation. All participants must be able to consent or have parents who can give parental permission in the case of a child patient.

Patients with one of four major cardiomyopathy

subtypes in both familial and non-familial form will be eligible for the study: HCM, DCM, ARVC, and RCM. Also, patients with biopsy proved myocarditis or an abnormal CMR will be enrolled. All types of cardiomyopathy and myocarditis must fulfill standard diagnostic criteria based on ESC guidelines mentioned below.

Identification and recruitment

RCMR consists of 4 patient's entry points: 1) Echocardiography department.2) CMR department. 3) Outpatient clinics. 4) Inpatients clinics

The research staff at the site will enroll potentially eligible subjects and ask them about their willingness to participate in this study. At the baseline study visit, the following will take place:

a) Clinical characterization including medical history and physical examination, symptoms, risk factors, family history of cardiomyopathy, Co-morbid conditions and current medication will be collected.

b) Electrocardiogram will perform for all patients in a relaxed position after a short time rest. ECGs will be saved in an appropriate format that can be analyzed by artificial intelligence.

c) All patients will undergo echocardiography, including 2D and 3D echocardiography.

d) Serum biomarkers including CBC, pro-BNP, cardiac enzymes, TFT, Blood biochemistry and lipid profile, LFT, CRP will be collected.

e) All patients will undergo the entire CMR and Holter. Also, the physician may request performing exercise tests for the patient.

f) Completion of a genetic family history questionnaire for all participants with or without a family history of cardiomyopathy and also a collection of a biological specimen- 15 ml of blood- based on precise protocol.

g) Patents with myocarditis, based on the physician's opinion, will undergo CMR and/or endomyocardial biopsy.

Follow-up

At each annual follow-up study visit, the following will take place: Survival status, hospitalization, Co-morbidities, Medications, and Procedures.

Participants will be given the option of allowing study personnel to contact them in-between visits for additional clarifications or to provide updates regarding Registry.

Cardiomyopathies and myocarditis diagnostic criteria

Dilated cardiomyopathy

Left ventricular ejection fraction <45% assessed by echocardiography or CMR and left ventricular end-diastolic diameter >117% of the predicted value corrected for age and body surface area that will be confirmed by other diagnostic workups such as thyroid function test, Liver function test, chest radiography, ECG, serum electrolytes test and family history (5-7).

Hypertrophic cardiomyopathy

In an adult, HCM is defined by a wall thickness ≥15 mm in one or more LV myocardial segments-assessed by echocardiography or CMR. As in adults, the Diagnosis of HCM requires an LV wall thickness more than two standard deviations greater than the predicted mean (z-score>2, where a z-score is defined as the number of standard deviations from the population mean) (7-9).

Arrhythmogenic right ventricular cardiomyopathy

Right ventricular functional and structural abnormalities were identified by echocardiography, CMR, and RV angiography. In ECG, there are repolarization and depolarization abnormalities. Fibro-fatty replacement of the right ventricular myocardium and Arrhythmias with the origin of the right ventricle are other diagnostic criteria (7,10,11).

Restrictive cardiomyopathy

RCM should be diagnosed only when there is objective evidence for elevated left ventricular filling pressure, based on conventional echocardiographic Doppler or invasive hemodynamic measurements in patients with a left ventricular ejection fraction >0.45, normal left ventricular wall thickness (corrected for gender and body size) and no evidence of pericardial constriction (7).

Myocarditis

Biopsy proven myocarditis: ≥14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of CD3 positive T-lymphocytes ≥7 cells/mm^2.

Clinically suspected myocarditis: abnormal CMR accompanied by clinical presentation, in the absence of significant coronary artery disease (stenosis ≥50%) or other known cardiovascular disease (7,12).

Study procedures-descriptions

CMR methods

All patients will undergo the entire CMR protocol to assure the correct assessment of LV volumes, mass, hypertrophy distribution, LGE (regional, patchy fibrosis), assessing vascular changes underlying coronary artery disease and measurement of diffuse fibrosis using native and post-contrast T1 mapping at specific time points as well as assessing various tissue pathologic changes, thus, prognosis in heart failure. CMR will be performed at 1.5 Tesla on magnetic resonance systems from the 3 primary vendors (General Electric, Philips Medical Systems, and Siemens Healthcare)

Echocardiographic assessment

Echocardiographic assessment will be performed for all patients as an essential approach to Diagnosis of cardiomyopathy and to decide on specific therapeutic strategies. Assessment of left ventricular wall thickness, contractile dysfunction, degree of left ventricular dilatation or left ventricular hypertrophy, pericardial effusion, dyssynchrony, systolic and diastolic function, assessment of the mitral valve and left ventricular outflow tract obstruction, concentric LVH, and assessment of right-side heart will be evaluated by 2D and/or 3D echocardiography.

An EPIQ 7 ultrasound scanner (Philips Ultrasound, WA, USA) will be used to conduct 2D-TEE and 3D-TEE. The standard 2D transthoracic echocardiographic examination will be performed using the Affiniti 70 (Philips Ultrasound, WA, USA). Using 2D images taken from the left ventricular long-axis view, the left ventricular end-diastolic and end-systolic as well as left atrial (LA) diameters will be determined.

12-lead electrocardiography

The standard 12-lead ECG will be performed at baseline visit in all individuals in order to find LVH, ST- and T-wave abnormalities, pathological Q-waves, and arrhythmias.

Laboratory tests

Laboratory test including hematology, glucose, cardiac enzymes (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, high sensitivity cardiac troponin T (hs-cTnT)), renal and liver function tests, electrolytes and uric acid, N-terminal pro-brain natriuretic peptide (NT-proBNP), Thyroid function tests, blood biochemistry will be assessed in the laboratory by specific types of equipment.

Sample size

Considering the explorative and observational nature of the current study, no formal sample size calculation has been performed. However, the current study is aiming at enrolling the following sample patients: 10000 cardiomyopathy and myocarditis and 3000 pediatrics. Obviously, the numbers need to answer scientific questions conclusively will depend on the outcomes.

Data analysis

The analysis of registry data will lead to aggregated reports summarizing the epidemiology of cardiomyopathies and myocarditis, as well as treatment and outcomes. Prior to analysis and reporting, a statistical analysis plan (SAP) will be created by in charge epidemiologist and approved by the steering committee.

Data transmission, storage, and confidentiality

Data will be transferred to the Registry Data Coordinating Center through a secure, electronic web-based data collection system named REGISTRY. Centralized registry data security includes password-protected login to the REGISTRY system and access provided only to Registry Data Coordinating Center personnel authorized as part of the Registry.

Any given site investigator in Registry is allowed to see only data about the participants who have collected and registered themselves. Central Coordination is allowed to view all data for checking, quality control and monitoring. Central Coordination statistically evaluates the whole data set after permission of the steering committee. The whole database is saved on a server.

Quality control

The database incorporates automated logic checks to prevent out-of-range values being entered or to feedback warnings to users when data are out of range. There will be additional monitoring to check main documents and ˪ow to enter data. During the site visits, the study monitor should review original patient documents and compare them with the electronic CRF. Between on-site monitoring visits the monitor should regularly check the electronic data for completeness and clarity of the data. Missing data will be marked. The random audit will also be conducted at study sites.

Discussion

Health policymakers and professionals, researchers and physicians are daily facing the challenge to

prioritize their activities in order to get the best results in different areas of their responsibilities. They can only make as good informed decisions by using data with high quality and acceptable availability (13).

A patient registry as a powerful tool to collect uniform data and evaluate specified outcomes for a population has served as an important source of the data needed to assess clinical proficiency or assess policy implications on national and international level. Registries are designed for patients having the same Diagnosis with sharing characteristics (symptoms, clinical presentation, implanted device, medical and surgical outcomes, risk of developing a disease, diagnostic/therapeutic equipment outcomes) (14).

In cardiomyopathy and myocarditis, knowing the natural history of disease and their epidemiological pattern in each population provide the information required for health service planning and improvement of therapies. Because these diseases have a substantial genetic component, they may have various presentations and outcomes in different populations. But in Iranian population, has largely been a blind spot to study the natural history of theses disease. RCMR aimed to determine clinical characteristics, natural history, current therapeutic approaches, response to treatment, and long-term outcomes of patients with cardiomyopathy and myocarditis and to decrease limitations in existing evidence to improve anticipation RCMR collects prospectively and systematically clinical data (e.g., clinical traits, family history, demographical data , treatment, and long term outcomes) with access to current standards for diagnostic methods and clinical follow-up of patients as well as therapeutic approaches currently employed for patients with different forms of cardiomyopathy and myocarditis.

RCMR has been considered as a long-term project with specified research approaches to advance the treatment of cardiomyopathy and myocarditis while protecting research participants privacy. RCMR builds on strong collaborative relationships among different clinical specialties, including heart failure, congenital heart disease, electrophysiology, echocardiography, cardiac MR, radiology, cardiac intervention, pathology, medical and clinical laboratory science, cardiac surgery, and pediatric cardiology in one hand and researchers and statisticians on the other hand under the supervision of research deputy.

RCMR will provide an ongoing observational study for eligible subjects and initially take place as a single center in the Rajaie cardiovascular medical and research center, and will then become multi-centered, and then there will be a national registry.

The clinical database on cardiomyopathy and myocarditis to be collected for the RCMR study will be used for a variety of different analyses. The design of RCMR places no limit on the sample size to be collected in which the study will be completed.

The ultimate objective of RCMR is providing high-quality research that can contribute to evidence-based guidelines and have an impact on patient care, in Rajaie cardiovascular and medical center as a tertiary center and then, expanding it across the country and turning it into a national registry.

The Rajaie Cardiomyopathy and Myocarditis Registry aims to recruit 10000 patients during 5 years and, therefore, to provide the most detailed analysis of the natural history and management of all types of cardiomyopathies and myocarditis in Iranian population to date.

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