Outlook on Dilated Cardiomyopathy

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Dilated cardiomyopathy (DCM) is characterized as a disorder of the heart muscle. It is distinguished by the widening/dilation of the left ventricle of the heart with left ventricular or biventricular systolic dysfunction. Contractile functioning of the left ventricle is highly compromised due to dilation. However, in some cases of DCM, the right ventricle is also dilated. Dilated cardiomyopathy (DCM) remains an enigmatic cardiovascular disease (CVD) condition characterized by contractile dysfunction of the myocardium due to dilation of the ventricles. DCM is one of the major forms of CVD contributing to heart failure. Dilation of the left or both ventricles with systolic dysfunction, not explained by known causes, is a hallmark of DCM. Progression of DCM leads to heart failure. Genetic and various other factors greatly contribute to the development of DCM, but the etiology has still remained elusive in a large number of cases.

Keywords: dilated cardiomyopathy (DCM) ; heart failure ; gene ; biomarkers ; mechanism ; treatment ; proteomics ; lipidomics

1. Causes of DCM

1.1. Causes of DCM in Children and Newborns

1.1.1. Myocarditis

Virus, allergens, toxins and autoimmune responses are responsible for myocardial damage [1]. This damage, caused by inflammation in general, is evidenced by the infiltration of immune cells into the myocardium associated with the degeneration and necrosis of myocytes during myocarditis. Importantly, histological evidence along with a specific threshold of leucocytes, monocytes and T-lymphocytes defines the myocarditis status [1][2][3][4]. Viral myocarditis is a common cause of Dilated cardiomyopathy (DCM). Coxsackie B virus infection has a high tendency to lead to DCM. Coxsackie B is categorized under the picornavirus family and enterovirus genus. It also has a close association with echovirus, poliovirus, and rhinovirus. Other viruses are also found to contribute to DCM. Coxsackie (A, B), Herpes simplex, Epstein-Barr virus, Rubeola, Coronavirus, Adenovirus, Cytomegalovirus, Mumps, Vaccinia, Hepatitis B, Influenza (A, B), Varicella-zoster, Rubella, HIV and rabies viruses cause myocarditis that leads to the DCM [5].

1.1.2. Selenium Deficiency

Selenium is one of the trace elements present in animal bodies. Selenium is an important element of selenoproteins which play a crucial role in various endocrine, immune, and reproductive processes. Glutathione peroxidases (*GSH-Px*) is a selenoprotein that inactivates peroxidase. Selenium is useful in cardiomyocytes for the function of the antioxidant defense mechanism and a deficiency of selenium can lead to DCM [6].

1.1.3. Malformation in Pulmonary Arteriovenous

Pulmonary arteriovenous malformation (PAVM) is a condition of anomalous communication between veins and pulmonary arteries. Congenital pulmonary arteriovenous malformations have a close relation with hereditary hemorrhage telangiectasia. The shunting of blood from the pulmonary artery to veins causes the delivery of low oxygen to the heart. Shunting of blood causes hypoxia which leads to pulmonary hypertension and imparts a high load on the left ventricle resulting in DCM causing a reduced ejection fraction [7]. However, congenital heart diseases should be diagnosed to understand the overlapping contributory phenotypes of the DCM pathology in patients.

1.1.4. Endocardial Fibroelastosis

Endocardial fibroelastosis is caused by the deposition of collagen and fibroelastin fibers in the endocardium. The mitral valve leaflet is thickened, and the left ventricle is dilated in endocardial fibroelastin. Over a period of time, it develops into DCM [8].

1.1.5. Noncompacted Myocardium

Noncompacted myocardium is associated with the regional thickness of the ventricular wall and it can lead to heart failure [9]. Mutations in the protein-encoding genes of tafazzin, lamin, actin, titin and others are involved in non-compact myocardium disease. These gene mutations eventually lead to DCM and heart failure.

1.1.6. Calcium Deficiency

Calcium deficiency causes irreversible DCM in infants. Calcium is essential for myocardial contraction. A deficiency of calcium in infants affects myocardial contractility [10].

1.1.7. Idiopathic DCM (IDCM)

IDCM contributes to 50 to 70% of the total number of cases of DCM in children [11]. Many cases of IDCM are assumed to have genetic causes. In a number of cases, IDCM is reclassified as familial DCM after family investigation and testing. There is no specific observable characteristic difference present between familial DCM and idiopathic DCM [11].

1.1.8. Barth Syndrome

Barth syndrome is a heart muscle syndrome caused by mutation in the tazzafin protein-encoding TAZ (*G4.5*) gene [12]. It is mostly present in males and it is often present from birth. It is characterized by muscle dilation and skeletal myopathy. In Barth syndrome, the heart muscles fail to perform the movement function properly. Children with Barth syndrome find it hard to move or crawl and they feel very tired even after little amount of effort. In many cases, Barth syndrome goes unnoticed in the early life of a patient. The development of noticeable symptoms varies greatly from person to person [13].

1.1.9. Familial/Genetic Pediatric DCM

Genetic causes are one of the major reasons for the occurrence of DCM. There are similarities in the genetic causes of newborns and adults. Rampersaud et al. [14] studied 41 cases of pediatric DCM. They identified 15 genes associated with DCM pediatric patients. Out of these 15 genes, 9 genes (*MYH7*, *SCN5A*, *TNNT2*, *LMNA*, *MYBPC3*, *MYH6*, *TNNC1*, *TNNI3* and *TPM1*) are also known to cause DCM in adults. Recently, Khan et al. [15] did a cohort study on 109 pediatric patients and found that *TTN* (Titin) truncation was the most prevalent cause of genetic DCM in pediatric patients. Along with *TTN*tv, genetic variations (mutation) were also detected in *MYH7* among pediatric DCM patients.

1.2. Causes of DCM in Adults/Adolescents

1.2.1. Familial/Genetic

It is estimated that 30–50% of DCM cases fall under this category [16]. DCM is highly linked with autosomal dominant inheritance, but X-linked and autosomal recessive inheritance has also been found to be associated with DCM. Mutations in the cytoskeletal and sarcomeric genes of cardiomyocytes are considered to be responsible for DCM [16]. Cytoskeletal genes including *TTN* (titin), *DES* (desmin), *LMNA* (lamin A/C), *ABLIM1* (actin binding LIM domain protein), *ACTN2* (α-actinin-2), *NEBL* (nebulette), *MYPN* (myopalladin), *SGCD* (δ sarcoglycan) and *ZASP* (Z band alternatively spliced PDZ domain protein) are involved in DCM [17]. Mutations in sarcomeric genes including *ACTC1* (cardiac actin alpha), *TNNT2*, *TNNI3*, *TNNC1* (troponin T2, I3 and C1), *MHY7* (β- myosin heavy chain), *TPM1* (tropomyosin-1), *PLN* (phospholamban), *MYBPC3* (myosin binding protein C) and *SCN5A* (Sodium channel protein type 5 subunit alpha) are associated with DCM (**Table 1**).

Table 1. Mutations in cytoskeletal and sarcomeric protein-coding genes are majorly associated with DCM [16][17][18][19].

Cytoskeletal and Sarcomeric Genes	
Titin (*TTN*)	**Cardiac actin alpha**
Desmin (*DES*)	**Troponin T2, I3, C1 (*TNNT2*, *TNNI3*, *TNNC1*)**
Lamin A/C (*LMNA*)	**β-myosin heavy chain (*MHY7*)**
α-actinin-2 (*ACTN2*)	**Tropomyosin-1 (*TPM1*)**
Actin binding LIM domain protein (*ABLIM1*)	**Phospholamban (*PLN*)**
Nebulette (*NEBL*)	**Myosin binding protein C (*MYBPC3*)**
Myopalladin (*MYPN*)	**Sodium channel protein type 5 subunit alpha (*SCN5A*)**

Cytoskeletal and Sarcomeric Genes	
Filamin C (*FLNC*)	BCL2-associated athanogene 3 (*BAG3*)
δ sarcoglycan (*SGCD*)	
Vinculin (*VCL*)	
Z band alternatively spliced PDZ domain protein (*ZASP*)	
Dystrophin gene (*DMD*)	

1.2.2. Alcohol

A daily consumption of alcohol of more than 35.2 mL in males and 17.6 mL in females can cause alcohol cardiomyopathy [20]. Although it remains debatable that a low consumption of alcohol can be useful in coronary artery disease (CAD), hemorrhagic stroke and heart failure, alcohol abuse increases blood pressure and adversely affects the immune system, which increases the chances of myocarditis [20]. Carbohydrate-deficient transferrin and elevated levels of liver enzyme with cardiomyopathy are diagnostic measures of alcohol-induced cardiomyopathy [20].

1.2.3. Myocarditis

Myocarditis affects both at early age and adult age due to several virus-mediated infections. The mode of action of myocarditis remains the same at all stages of life.

1.2.4. Tachycardiomyopathy

Tachycardiomyopathy, also known as tachycardia-induced cardiomyopathy, is a left ventricle disorder. It is a cardiac condition which can be partially or completely reversed. If tachyarrhythmia is controlled then tachycardiomyopathy can also be reversed to normal stage [21].

1.2.5. Mitochondrial Diseases

Mitochondrial disorders including NADH-coenzyme Q reductase (complex I) deficiency, deficiency of cytochrome C oxidase, lactic acidosis, myoclonic epilepsy with ragged red fibers (MERFF), Kearns–Sayre syndrome, encephalopathy associated with mitochondria, and most importantly carnitine palmitoyl transferase II deficiency, significantly contribute to developing DCM [22].

1.2.6. Cardiomyopathy Associated with Right Ventricular Arrhythmia

Although less prevalent, it is a life-threatening condition entailing sudden death in young and sports persons. Mutation of the desmosomal protein gene leads to this disease which is now considered as genetic myocardial dystrophy [23].

1.2.7. Eosinophilic Myocarditis

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is characterized by systemic vasculitis. This vasculitis affects the small and medium sized blood vessels [24]. The effects of this disease in the heart are dangerous and can lead to heart failure [25]. Eosinophilic myocarditis is diagnosed with left ventricle enlargement and decreased systolic function. If eosinophilic myocarditis is caused by Churg-Strauss syndrome then treatment of the Churg-Strauss syndrome can reverse the eosinophilic myocarditis to the normal stage [26].

1.2.8. Toxins

Over-exposure to heavy metal toxins can lead to DCM. Lead (Pb), cobalt (Co) and arsenic (As) over-intoxication can lead to DCM. Iron overload is also found to cause DCM [27]. Under certain genetic and metabolic disorders, the amount of circulating iron exceeds the handling capacity of transferrin. Free, unbound iron is a potent free radical which causes oxidative damage to the cardiomyocytes. Lead is a toxin which attacks the cardiovascular system adversely. Cobalt is useful in the production of red blood cells, but a very high amount of blood cells due to a higher level of cobalt can affect the heart rate by interfering with calcium binding to sarcolemma [27]. Thus, it causes trouble in contractility in the heart. Arsenic is a toxin which directly attacks cardiac muscles. It dilates cardiac capillaries and it induces DCM [27].

1.2.9. Peripartum Cardiomyopathy

It is a life-threatening disease. It is developed during pregnancy in females. It severely affects females during late pregnancy or the puerperium phase. In peripartum DCM, cardiac failure can be observed towards the end of the gestation

period to the 5-month postpartum period [28].

1.2.10. Endocrinopathy

A hormonal imbalance in the body can lead to the development of DCM. An imbalance of the thyroid hormones leads to heart disorders. Tachycardia and palpitations are common in patients with thyroid hormone imbalance [29]. The catecholamine secretion from tumors induces cardiac remodeling [30]. A low level of insulin causing persistent hyperglycemia severely compromises cardiac functions leading to DCM or other cardiomyopathies [31].

1.2.11. Nutritional Deficiency

Low levels of thiamine (B_6), carnitine deficiency and hypophosphatemia have a correlation with DCM progression. Nutritional deficiency leads to the abnormal functioning of cardiac muscles and long-term nutritional deficiencies can lead to DCM and other disorders [32].

2. Diagnosis of DCM

2.1. Clinical Investigation

Clinical investigation is the front-line diagnosis procedure. Many patients do not manifest diagnostic symptoms until they are at the advanced stage of heart failure [33]. Decreased cardiac output and arrhythmia are general symptoms of DCM but many individuals with DCM are asymptomatic. Family history plays a significant role in DCM [34]. The investigation of family history of disease includes type 2 diabetes, epilepsy, deafness and other metabolic disorders [35].

2.2. Electrocardiography (ECG)

In patients with DCM, the electrocardiograms are not generally normal and patients with extensive fibrosis in the left ventricle are observed with isolated T wave change to the septal Q wave [36]. Delay in atrioventricular conduction and a bundle branch block are also likely to be observed [36]. Due to atrial fibrillation, sinus tachycardia and supraventricular arrhythmia can be observed [37].

2.3. Echocardiography

Echocardiography is most essential and one of the gold-standard techniques in the diagnosis of DCM. The echo diagnostic criteria of DCM includes the left ventricle area >112% which indicates dilation of the left ventricle. A fraction shortening <25% indicates abnormal systolic function. A left ventricle area >117% is a criterion for screening familial DCM [38].

2.4. Magnetic Resonance Imaging (MRI)

MRI is useful in determining chamber dimensions, wall thickness and ventricle mass. MRI is also useful in the assessment of flow rate, abnormality in wall motion, edema, fibrosis and hyperemia [39].

2.5. Serological Test for Virus

Serological testing for virus by specific IgM antibody titer test can be useful in detecting viral myocarditis [40].

2.6. Endomyocardial Biopsy

This is the most definitive method for the diagnosis of DCM. An endomyocardial biopsy can diagnose patients who cannot be screened through other methods. Endomyocardial biopsy can detect various myocardial diseases [41]. However, this is an invasive, costly method warranting specialized expertise. Hence, it has limitations for screening in general population.

2.7. Clinical Genetics of DCM

Genetic testing is now widely used in the detection of DCM. Genetic testing is crucial in the case of asymptomatic patients for better management and early intervention of subjects. Family genetic history using pedigree analysis has remained a classical approach in the diagnosis of genetic DCM. Pedigree analysis can help in the diagnosis of mutation in family-specific genes by genetic testing. However, it has remained a challenge to ascertain the specific genes causing DCM. Moreover, more than 100 genes have been reported to be involved in the etiology of DCM [42]. Commercial laboratories are using a gene panel (~60 genes) to test the susceptibility of developing DCM in different populations. Recently, Jordan et al. [42] evaluated the potential of a large gene panel for DCM prediction and summarized 12 definitive (strongly

associated, included in **Table 1** and shown in **Figure 1**) genes to be exclusively associated with the DCM pathophysiology, not hypertrophic cardiomyopathy (HCM) or any other cardiomyopathy. The panel of these 12 genes should be evaluated across different populations to be implemented as a standard genetic test to screen for DCM patients [19][43].

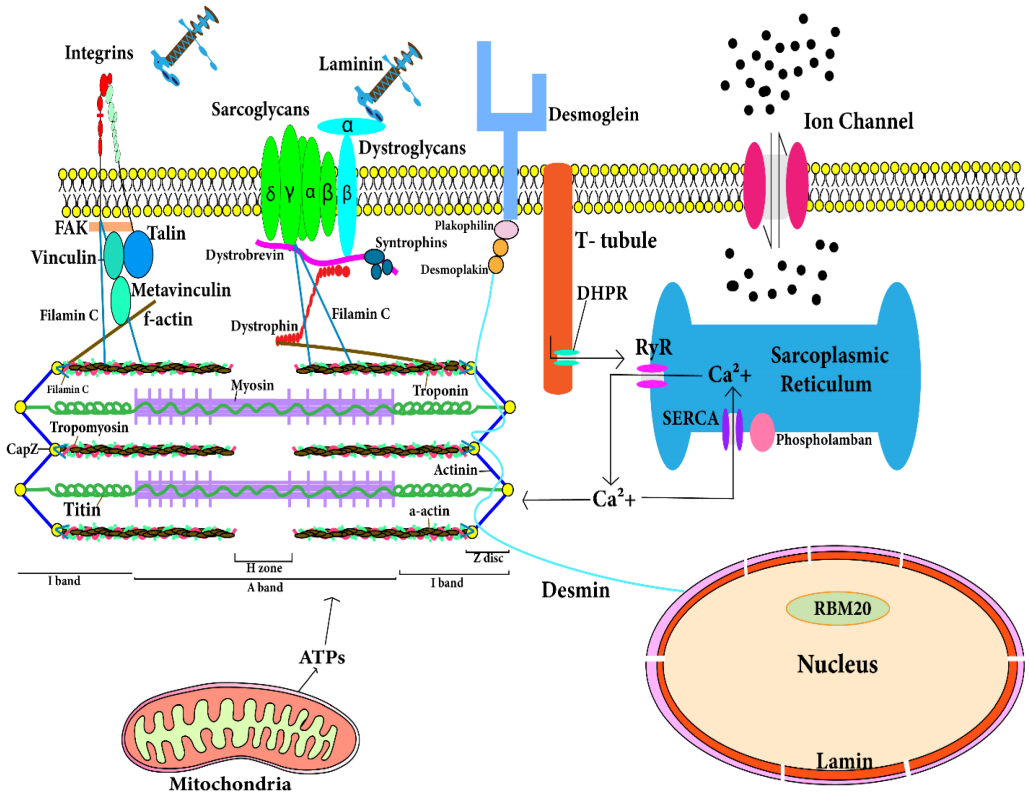

Figure 1. Location of proteins in cardiomyocytes that are responsible for development of dilated cardiomyopathy. The figure depicts the spatial location of the cytosolic and sarcomeric proteins encoded by corresponding genes. Mutations in these genes contribute to development of dilated cardiomyopathy. The T-tubule has a large number of ion channels and transporters. T-tubule regulates the calcium concentration in cardiomyocytes and transmits the action potential into the cardiomyocyte. RyR (ryanodine receptor) in sarcoplasmic reticulum (SR) of cardiomyocyte interacts with T-tubule for action potential transmission and RyR is responsible for release of stored calcium from SR. Calcium and ATPs are utilized by sarcomere in contraction. After contraction, calcium released from sarcomere is stored in SR through SERCA. Sarcolemmal and cytoskeletal proteins maintain architecture and functions of cardiomyocytes. Mutation in any of these protein-encoding genes leads to dilated cardiomyopathy.

2.8. Pathological Tests for DCM Diagnosis

Several pathological tests in isolation or in combination are performed in order to detect the clinical severity of DCM patients (**Table 2**) [6][32][44][45][46].

Table 2. Pathological tests for DCM diagnosis [6][32][44][45][46].

Pathological Tests	Other Tests in Specific Indications
Erythrocyte sedimentation rate (ESR)	Coronary angiography
Viral serology	Blood content tests—carnitine, pyruvate, lactate, autoantibodies, selenium, acylcarnitine profile and drug screening.
Creatine kinase (CK)	Red cell transketolase (beri beri)
Liver function tests	Urine
Renal function	Enteroviruses test
Serum ferritin/iron/transferring	Infective screening (HIV/hepatitis C)
Thyroid function tests	Organic acid/amino acids

2.9. Protein Biomarkers of DCM

There are alterations in the protein content in the heart during the development of DCM. This alteration can be detected by proteomic techniques [47]. These alterations in the protein content indicate the progression of DCM. Various gene mutations work as genetic biomarkers for the diagnosis of DCM, in the same way that proteins are generally used as biomarkers of DCM.

2.9.1. Brain Natriuretic Peptide (BNP)

Brain natriuretic peptide indicates stress on the ventricles. Brain natriuretic peptide levels predict DCM as well as heart failure. *BNP* levels accurately diagnose DCM and heart failure. Brain natriuretic peptide can also be used to assess the effectiveness of a heart therapy [48].

2.9.2. ST2

ST2 is a cardiac biomarker, which is a member of the interleukin-1 receptor family. ST2 is released by cardiomyocytes in stress conditions. The presence of ST2 indicates tissue fibrosis, cardiac remodeling and abnormality in the heart. ST2 can diagnose a heart abnormality at an earlier stage than the brain natriuretic peptide [49].

2.9.3. Troponins T, I

Troponins T and I are sensitive biomarkers of heart failure. A modest increase in the serum level of troponins T and I predict abnormality in the heart. Most of heart failure patients have elevated levels of high sensitivity troponin in the serum [50].

2.9.4. Procollagen Type III

Collagen also works as heart failure biomarker. Elevated levels of collagen predict abnormality in the heart. Procollagen type III independently predicts progression of heart diseases [51].

2.9.5. Matrix Metalloproteinase (MMP)

Matrix metalloproteinases work as biomarkers for DCM and heart failure. Elevated levels of matrix metalloproteinase predict cardiac dilation and a decrease in ejection fraction. Elevated levels of *MMP*-2, -7, -8, and -9 are found in children with DCM [52].

2.9.6. Galectin-3

Under stressed conditions, activated macrophages produce galectin-3 protein. Galectin-3 protein predicts abnormality in the heart. Galectin-3 in combination with N-terminal brain natriuretic peptide (proBNP) is the best biomarker for the diagnosis of acute heart failure. It is also useful in assessing the effectiveness of a therapy in individuals with heart disease [53].

3. Treatment Strategies of DCM

There is no treatment available to permanently cure or ameliorate the DCM condition, but several treatment regimens are clinically practiced to restrict the progression of DCM and further reduce the symptoms. The current state-of-the-art therapeutic regimens described below aim to prevent heart failure and thromboembolism.

3.1. Angiotensin-Converting Enzyme (ACE) Inhibitors

In all etiologies of heart failure, the activation of the renin angiotensin aldosterone system (RAAS) is significant. To block this pathway, ACE inhibitors are used. These inhibitors are found to relieve dyspnea and reduce heart disease progression. ACE inhibitors work by preventing the formation of angiotensin II which is a vasoconstrictor that inhibits the hydrolysis of bradykinin, which is a vasodilator [54]. Thus, ACE inhibitors prevent blood load on blood vessels and decrease blood pressure. Commonly used ACE inhibitor drugs are Benazepril, Perindopril, Trandolapril, Zofenopril, and Ramipril. Adverse effects of ACE inhibitors are also observed in some patients [55]. Impairment in renal function is a major side effect, hypotension and cough are also adverse effects of the use of ACE inhibitors [55].

3.2. Diuretics

Diuretic drugs are useful in treating heart disease. Diuretics increase the excretion of water and salts from the body, which lowers the pumping load from the heart. These drugs work by inhibiting the antidiuretic hormone vasopressin and they

work to reduce the blood pressure, swelling, and water buildup [56][57]. The side effects of diuretics include increased peeing, tiredness, weakness, muscle cramps, blurred vision, headache, increased sweating, and dehydration.

3.3. Angiotensin II (Ang-II) Receptor Antagonists

These are angiotensin II receptor blocking drugs. These drugs bind to angiotensin II receptors and actively inhibit their function. Thus, arteriolar contraction and sodium retention is prevented by angiotensin II receptor antagonists [58].

3.4. Beta Blockers

Beta-blockers are widely used to control heart disease. Beta-blockers are efficient in temporarily reducing blood pressure, angina, arrhythmia, anxiety, migraine, glaucoma, and overactive thyroid [59]. Beta blockers are useful in preventing heart attack [60]. Adrenaline and noradrenaline hormones are responsible for inducing the fight or flight response in the body in the presence of any danger. These hormones increase oxygen demand, heartbeat, arrhythmia, blood pressure, anxiety, sweating and palpitation in the body [60]. These hormones excessively increase the load on the heart. Beta blockers block the action of these hormones by competitively binding with the beta-adrenergic receptors of endogenous catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) hormones. B_1-adrenergic receptors are found in the cells of the heart which are blocked by beta blockers [61].

3.5. Spironolactone

Spironolactones are used to lower blood pressure. Spironolactones are useful in preventing heart failure and in some cases, they are also useful in managing edema. Aldosterone is present in high amounts in DCM patients, retains sodium inside the body, excretes potassium and causes baroreceptor dysfunction [62]. Mineralocorticoid receptors in the distal convoluted tubule are competitively inhibited by spironolactones [62]. This inhibition increases water and sodium excretion and potassium retention [62].

3.6. SGLT2 Inhibitors (SGLT2i)

In the comorbid condition of diabetes mellitus and cardiovascular disease, SGLT2 inhibitors are quite useful. These molecular inhibitors of sodium-glucose-co-transporter 2 reduce the blood glucose level by promoting the urinary excretion of glucose. The unique mode of action of SGLT2 inhibitors results in glycosuria. SGLT2 inhibitors show diuretic and natriuretic actions. These actions help in decreasing blood pressure and plasma volume. A decrease in albuminuria and the glomerular infiltration rate is also associated with SGLT2 inhibitor treatment [63]. SGLT2 are becoming the primary choice for treatment in patients having diabetes with diabetic kidney disease (DKD) and cardiovascular diseases [64]. Empagliflozin, canagliflozin and dapagliflozin are available as SGLT2 inhibitor drugs used in clinical practice.

3.7. Potential Novel Treatments of DCM

3.7.1. Cytokine Antagonists

Degraded myocardium, activated macrophages and T cells secrete tumor necrosis factor α (TNF-α) and other secreted proinflammatory cytokines to promote the progression of cardiomyopathy [65]. The pentoxifylline drug is a xanthine derivative which actively suppresses the production of TNF-α [66]. Endothelin peptides are produced in high amounts in DCM patients and these peptides contribute to vasoconstriction leading to increased blood pressure. Bosentan is an endothelin antagonist which helps in lowering the blood pressure [67].

3.7.2. Anticoagulants

In patients with a history of thromboembolism, high ventricular dilation, and severe systolic dysfunction, anticoagulants are used in treatment [68]. Blood thinner drugs prevent stroke in people with severe heart disease. Warfarin is an anticoagulant drug that prevents blood coagulation by blocking the enzyme vitamin K epoxide reductase.

3.7.3. Natriuretic Peptides

Atrial natriuretic peptides (*ANP*) are natural vasodilators and diuretics which are secreted by atrial myocytes in response to stretch/stress or other stimulations [69]. These may be useful in DCM. Tolerance against these peptides is gained in a short time so these cannot be administrated for long periods and research is needed to make drugs based on them for use in heart disease.

3.7.4. Stem Cell Therapy

Stem cell therapy is an exciting newer approach studied for the treatment of DCM. Autologous bone marrow cell therapy for DCM in the short term (6 months) and long term (3 years) showed beneficial results [70]. In the future, stem cell therapy could be highly useful in the treatment of DCM.

3.7.5. Clinical Trials

Drugs undergoing clinical trials for DCM in the United States are listed in **Table 3**.

Table 3. Description of drugs for dilated cardiomyopathy undergoing clinical trials in the United States [71].

Drug	Title of Project	Description	Disease or Condition	Location
ARRY-371797, (p38 inhibitor)	A rollover study of ARRY-371797 in patients with LMNA-related dilated cardiomyopathy	Assessment of effectiveness of drug ARRY-371797 is being investigated in this clinical trial.	LMNA-related dilated cardiomyopathy	University of Colorado Aurora, Colorado, United States Johns Hopkins University Baltimore, Maryland, United States
ARRY-371797	A study of ARRY-371797 in patients with symptomatic dilated cardiomyopathy due to a lamin A/C gene mutation	This study is a placebo controlled, dose-dependent efficacy assessment of ARRY-371797 drug on LMNA gene mutation dilated cardiomyopathy patients.	Lamin A/C gene mutation dilated cardiomyopathy	Pfizer Investigational Site Birmingham, Alabama, United States. CB Flock Research Corporation Mobile, Alabama, United States, and 64 more.
Ivabradine	Pulse reduction on beta-blocker and Ivabradine therapy	Ivabradine improves ejection fraction by reducing heart rate independently from beta-blockade.	Dilated cardiomyopathy ventricular remodeling electrical remodeling	University of Colorado Anschutz Medical Campus Aurora, Colorado, United States The Ohio State University Wexner Medical Center Columbus, Ohio, United States
Ifetroban	Oral Ifetroban in subjects with Duchenne muscular dystrophy (DMD)	X-linked Duchenne muscular dystrophy (DMD) is a fatal genetic disorder. This lacks effective treatment therapy. Ifetroban is assessed in this study for the treatment of DMD.	Duchenne muscular dystrophy cardiomyopathy dilated cardiomyopathy	Mattel Children's Hospital Los Angeles, California, United States and 3 more.

3.8. Assisting Devices and Mechanical Support

3.8.1. Partial Left Ventriculectomy (PLV)

PLV is used in the treatment of DCM. It reduces heart wall pressure by resection of a portion of the left ventricle which lowers cardiac volume [72]. PLV is used on patients who are ready to receive a heart transplant but are unable to receive it [73].

3.8.2. Left Ventricular Assist Devices (LVADs)

LVADs are used in end stage heart failure patients. LVADs are used as a bridge to heart transplantation. Advanced LVADs can be used as a replacement of transplant [74].

3.8.3. Multisite Ventricular Pacing

Patients with DCM have abnormal left ventricle function. A delay in conduction of the left ventricle is also associated in the prolongation of conduction of the atrioventricle. The synchrony in the function is restored by dual-chamber pacing [75].

Single ventricular pacing is not considered sufficient, so biventricular pacing is used. Pacing is used in patients having a QRS duration of more than 150 ms [75].

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