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The Clinical Significance of Anti-Beta-1 Adrenergic Receptor Autoantibodies in Cardiac Disease

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Abstract Autoimmune response against myocardial antigens is evident in numerous heart diseases. Both the induction of an autoimmune response and the pathogenesis of autoimmune heart diseases are not fully understood. The humoral immune response may play an important role via induction of cardiomyocyte apoptosis, alteration of myocardial mechanical and electrophysiological functions, and activation of the complement system and cell-mediated cytotoxicity. Anti-β-1 adrenergic receptor antibodies appear to contribute to the pathogenesis of dilated cardiomyopathy, heart failure, and Chagas disease. Herein, we review the current knowledge relating to anti-β-1 adrenergic receptor antibodies: their potential role in heart diseases and the potential benefits of a targeted therapy against their apparently destructive effects. Patients with dilated cardiomyopathy with circulating stimulatory anti-β-1 adrenergic receptor autoantibodies are probably at a higher risk for adverse outcome and should be treated with adrenergic receptor antagonists, and possibly with immunotherapy. Further research is required to determine which patients will gain additional clinical benefits from anti-autoantibody-targeted therapy.

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Introduction

Autoimmune response against myocardial tissue may contribute to the pathogenesis of heart diseases such as dilated cardiomyopathy (DCM), heart failure, myocarditis, rheumatic fever, idiopathic recurrent pericarditis, and atherosclerosis. The mechanisms causing the autoimmune response in predisposed individuals are complex and not fully understood. Genetic, immune, hormonal, and environmental factors influence autoimmunity. In certain cases, the autoimmune response appears following a myocardial injury due to infection, toxins, ischemia, inflammation or other cardiotoxic factors, and exposure to autoantigens. Previous studies have reported that infections with specific viruses, parasites, or bacteria were found to cause an autoimmune reaction due to cross-reactivity between self-antigens and foreign antigens [1–8]. It is possible that autoimmune-mediated myocardial damage further accelerates exposure of self-antigens and subsequently, the autoimmune reaction [2]. The humoral immune response may play an important role in the pathogenesis of cardiac damage, both directly (by induction of apoptosis and alteration of myocardial function) or due to activation of the complement system and cell-mediated cytotoxicity. Although the role of certain autoantibodies may be unclear, autoantibodies are the hallmark of most autoimmune diseases [9–11].

Autoantibodies reactive with heart tissue were found in certain heart diseases. These autoantibodies can react with various cytoplasmic and endoplasmic antigens such as

receptors, contractile proteins, and other cellular or mitochondrial antigens [2, 12]. The findings of anti-cardiac autoantibodies and the identification of self-antigens presents *indirect* proof of autoimmunity. Nevertheless, the clinical relevance of these autoantibodies is uncertain. In many autoimmune diseases, autoantibodies may be detected in the serum, years before disease evolvement [13]. It is therefore unknown whether autoantibodies in heart disease appear due to an inappropriate autoimmune response following cardiac injury, or are caused by primary elevated autoantibodies without an obvious trigger or initial cardiac injury [14].

Myocardial Effects of Anti-β-1 Adrenergic Receptor Autoantibodies

In 1976, Sterin-Borda et al. reported that sera (containing circulating antibodies reactive with endocardium, blood vessels, and striated muscles) from specific patients with Chagas disease had a positive chrontropic in vitro effect on the atrium of rats [15]. This effect was prevented by administering the β-adrenergic receptor antagonist but not by administering the α-adrenergic receptor antagonist or anti-histamine agent. The authors suggested that a circulating antibody may induce an endogenous release of norepinephrine, or create a partial-agonist effect due to interaction with the β-adrenergic receptor (β-AR), or other indirect influences on the myocardial cells [15].

In 1989, Limas et al. found a substance suspected of being an antibody, taken from the serum of DCM patients, inhibited ligand binding to a β-AR present on myocardial cells of rats [16]. Later, that substance was found to be an anti-β-1 adrenergic receptor autoantibody (anti-β1AR-AAbs). β1-AR is a seven-transmembrane G-protein coupled membrane receptor, and when activated, it mediates a cardiac sympathetic response [17].

Anti-β1AR-AAbs autoantibodies may influence myocardial functions and possibly contribute to the pathogenesis of several cardiac diseases (i.e., myocarditis, dilated cardiomyopathy, ischemic cardiomyopathy, and Chagas disease), although the mechanisms remain uncertain.

Moreover, the mechanism by which anti-β1AR-AAbs are induced is unknown: either resulting from molecular mimicry between AR and antigens of infectious agents, or following exposure of autoantigens to the immune system [1]. In addition, it is also unknown whether some patients are prone to spontaneously produce anti-β1AR-AAbs due to immune dysfunction or genetic predisposition.

There are several screening methods for detecting anti-β1AR-AAbs and their effects, i.e., ELISA, Western blotting, functional assays by evaluating the effect on neonatal rat cardiomyocytes, surface plasmon resonance, and evaluation of the receptor-mediated signaling [cAMP levels and cAMP-dependent protein kinase A (PKA) activity] [18]. An association between anti-β1AR-AAbs and increased cAMP production was reported by Chiale et al. [19].

Studies have found that the only potentially active anti-β1AR-AAbs are those targeting the second extracellular loop, and in some cases, the first extracellular loop of the β1-AR [1, 20]. Antibodies directed against the N- or C-terminus, in contrast, have no biological effect on the receptor [21].

The mechanisms by which anti-β1AR-AAbs influence cardiomyocytes and cause adverse cellular effects are complex and not fully understood [22]. Anti-β1AR-AAbs activates the β1-AR and causes intracellular activation of the guanosine triphosphate-binding protein and adenylyl cyclase [20]. In addition, anti-β1AR-AAbs activate the extracellular signal-regulated kinase (ERK), 1/2 cascade *via* PKA, and Src-like tyrosine kinase activation in a dose-dependent manner. ERK cascade activation is also present following isoproterenol (a sympathomimetic beta adrenergic agonist) binding to β1-AR. However, the molecular mechanisms are different, except for PKA which is common to both. The ERK cascade may mediate cardiac hypertrophy and failure [23, 24]. Notably, cardiac hypertrophy was demonstrated to be associated with an increased risk of sudden death and malignant arrhythmias [25].

The anti-β1AR-AAbs causes an increase of L-type calcium current, calcium influx, prolongation of the plateau phase of the action potential (slightly lower than isoprenaline), and activation of the sodium/calcium exchanger. Moreover, it was found that transient outward- and delayed rectifier-potassium currents were decreased in rabbits following immunization against β1-AR. A secondary cardiac electrical instability and prolongation of the late repolarization phase may account for a higher risk of fatal ventricular arrhythmias [16, 20, 26, 27]. In a rabbit model, it was found that β1AR extracted from sera of patients with Chagas disease caused QT interval shortening [28]. It is well known that repolarization abnormalities may be associated with adverse consequences [29]. It was also found that sympathetic stimulation triggered activity of both early and delayed after-depolarizations and, subsequently, arrhythmic substrate [30]. When anti-β1AR-AAbs taken from certain DCM patients was added to an isolated cardiomyocytes culture, the results were different degrees of prolongation of action potential duration, demonstrating that individuals have autoantibodies with different activity and concentration in the serum [27]. Prolongation of the action potential duration was found both in human atrial and rat ventricular myocytes [28]. In contrast, anti-β1AR-

AAbs from patient with Chagas disease was reported to shorten the action potential duration of guinea pig M cells [28]. Medei et al. suggested that the differences may be related to different tissue responses or technical issues [28].

Anti-β1AR-AAbs act as allosteric regulators of receptor activity causing agonist, partial-agonist (observed in humans), or inverse-agonist (observed in animals) effects on the adrenergic receptor by affecting ligand binding and altering receptor conformation [20, 21, 31–33]. Anti-β1AR-AAbs may react with a different receptor activity state of the β1AR [1]. Functioning of anti-β1AR-AAbs depends on an immunoglobulin type (IgM or IgG) and the species from which it was extracted (i.e., human, rabbit, rat) [21]. Direct activation of β1-AR was achieved by anti-β1AR-AAbs, but not with Fab fragments of the same antibodies, indicating that receptor activation requires simultaneously the binding of two receptors [27].

Inhibition of dihydroalprenolol binding to β1-AR, due to IgG type anti-β1AR-AAbs antibodies was detected in 30–75% of DCM patients and 37% of patients with ischemic or valvular heart disease [34]. Anti-β1AR-AAbs were also found to inhibit isoproterenol binding to the AR [34]. It is undecided as to whether agonist or partial-agonist activity alters prognosis and clinical manifestations in heart disease [21].

Anti-β1AR-AAbs in vitro were found to have a positive chronotropic and inotropic effect on cardiomyocytes [34, 35] in addition to accelerating post-contraction relaxation (e.g., a positive lusitropic effect) [17]. The adrenergic stimulation effect of anti-β1AR-AAbs on cultured cardiomyocytes was sustained compared with other β-adrenergic agonists (>6 h compared with approximately 1 h in isoproterenol) [36]. The chronotropic effect of anti-β1AR-AAbs had on cultured neonatal rat cardiomyocytes was used in a bioassay to evaluate the presence and absence of anti-β1AR-AAbs [36]. It has been suggested that the stimulating effect that anti-β1AR-AAbs has on cardiomyocytes might cause deterioration of the contractile function in patients with ischemic or dilated cardiomyopathy [14, 21].

Cellular apoptosis is commonly found in DCM and other cardiac diseases. Continuous activation of the AR with isoprenaline may eventually lead to cellular apoptosis. Gao et al. demonstrated that anti-β1AR-AAbs promoted apoptosis in neonatal rat cardiomyocytes [37]. Anti-β1AR-AAbs may cause a direct toxic effect on myocardial cells by activation of caspases 3, 9, 12, and the apoptosis pathways, in a dose-dependent manner [2, 16, 32]. Anti-β1AR-AAbs also activates PKA which ultimately favors apoptosis, similar to the mechanism of catecholamine-induced cardiotoxicity [32]. The use of PKA inhibitor Rp-Adenosine-3 V, 5 V-cyclic monophosphothioate triethylamine, prevents the anti-β1AR-AAbs-induced apoptosis [32]. Other substances found to decrease apoptosis were adrenergic β-blockers, cAMP inhibitors, Z-VAD-FMK (pan-caspase inhibitor), and L-type calcium channel blockers [16, 17]. Endoplasmic reticulum stress and apoptosis may also be prevented by KN-93 and SB 203580 [38]. Ca^{2+}/calmodulin-dependent protein kinase II and p-38 mitogen-activated protein kinase activity may also promote apoptosis due to anti-β1AR-AAbs binding, which ultimately leads to activation of procaspase-12 [22, 39]. Apoptosis is also mediated by anti-β1AR-AAbs due to inhibition of phosphatidylinositol 3-kinase/Akt/STAT3 signaling pathway [39].

It should be emphasized that pathogenic effects of anti-β1AR-AAbs may be encountered even when small levels of autoantibodies are measured, due to about a 50% tissue distribution and highly potent cellular activity [14].

Healthy Individuals

Although anti-β1AR-AAbs were reported in several heart diseases, occurrence in healthy individuals has been reported by several authors. Similarly, other anti-heart autoantibodies (i.e., anti-cardiac troponin AAbs) have been reported in both healthy individuals and those suffering from heart disease [40]. Chiale et al. reported that none of the included 15 healthy individuals had circulating anti-β1AR-AAbs [41]. In another study, by Chiale et al., none of the ten included healthy individuals had detectable anti-β1AR-AAbs [19]. Magnusson et al. evaluated anti-β1AR-AAbs in 34 healthy blood donors and found that four patients had reactive AAbs [42]. Liu et al. reported that the occurrence of anti-β1AR-AAbs in 408 healthy individuals of various ages was 10% [43]. Also, the co-occurrence of anti-β1AR-AAbs and anti-M2-muscarinic receptors among anti-β1AR-AAbs-positive patients was 63.4% [43]. The healthy individuals in Liu et al. study had low titers of anti-β1AR-AAbs. An association between sero-positivity and increased age was also found [43]. Jahns et al. reported that less than 4% of 108 healthy included patients had AAbs reactive with AR domains, although functionally active AAbs was found in only one healthy patient [44]. It should be emphasized that measurements of anti-β1AR-AAbs may differ due to the methodology used. The clinical significance of sero-positive anti-β1AR-AAbs in asymptomatic or healthy individuals remains to be explored.

Dilated Cardiomyopathy

DCM is one of the main causes of heart disease in young adults [36] and is characterized by a dysfunctional and enlarged heart due to infection, cardiotoxic chemicals, drugs, or metabolic and muscular diseases [31]. Genetic mutations of myocyte structural proteins, consumption of

alcohol, or past treatment with chemotherapeutic agents accounts for about third of DCM cases [14]. In about 10% of these cases, cardiac dysfunction results from a chronic presentation of acute myocarditis [45]. Approximately 10–20% of myocarditis cases will progress to DCM [46]. A substantial number of DCM cases remain idiopathic, although it appears that autoimmunity plays a role in the pathogenesis [1, 2]. Circulating autoantibodies support the diagnosis of autoimmune-mediated DCM.

A criteria system for autoimmune-mediated DCM was recently proposed by our group [31]. Apart from autoantibodies, other immune abnormalities found in DCM were abnormal cell-mediated immunity and altered antigen presentation [16]. Several autoantibodies have been found in approximately 33% of DCM patients: anti-β1AR, anti-muscarinic receptor, anti-β and anti-α myosin heavy chains, anti-actin, laminin, and anti-troponin, anti-sarcolemmal and anti-myolemmal, anti-fibrillary and anti-interfibrillary antibodies, and anti-mitochondrial antibodies [47]. According to other reports, autoantibodies may be found in approximately 85% of DCM patients [16]. The role of anti-β1AR-AAbs in the pathogenesis of DCM and their importance as a therapeutic target are controversial.

Jahns et al. recently described a new receptor-directed autoimmune entity: anti-β1AR-AAbs-induced immune-mediated DCM [1]. Overall, the prevalence of anti-β1AR-AAbs in DCM patients was reported to be 26–95% [26], although lower ranges of 30–50% were reported as well [48]. The inconsistency among studies may be due to the lack of standardized measurement methods. According to a novel method of quantifying receptor-mediated signaling, high activators of anti-β1AR-AAbs against the second extracellular loop were present in approximately 33% of DCM patients. Low activators of anti-β1AR-AAbs against the first extracellular loop were found in approximately 36% of patients [18].

Inhibitory anti-β1AR and stimulatory anti-β1AR-AAbs were found in patients with idiopathic DCM (30–75% compared with less than 4–12% in healthy subjects according to ligand binding inhibition; 95% compared with 0% according to a bioassay, and 26% compared with 1% according to ELISA, respectively) [34, 47].

DCM induction in rats was achieved following immunization against β1-AR, accompanied with elevation of serum autoantibodies (presenting an *indirect proof* of the pathogenesis). Subsequently, DCM was induced in healthy rats by the passive transfer of autoantibodies from the rats that had developed DCM; hence, presenting *direct proof* of autoimmunity in DCM-induced rats [14, 34]. Similarly, DCM-like myocardial changes appeared in rabbits following immunization with a second AR extracellular loop-homologous peptide and subsequent development of anti-β1AR-AAbs [1, 32, 36].

The autoimmune process induced by the pathogenic autoantibodies is slow but progressive [14]. Caforio et al. [34] suggests that the chronotrophic effect of anti-β1AR-AAbs contributes to myocardial failure in DCM patients.

In some studies, anti-β1AR-AAbs were more frequently found in DCM patients with worse contractile functions or more advanced *New York Heart Association* (NYHA) functional class, while others found that anti-β1AR-AAbs-positive patients were not associated with a lower ejection function or higher NYHA functional class [30, 32, 49]. Others have reported that practically all DCM patients requiring mechanical cardiac support are seropositive for anti-β1AR-AAbs [36].

Higher anti-β1AR-AAbs levels were found to have negative prognostic effects in DCM patients [31], correlating with a higher risk of ventricular arrhythmias and sudden death [20, 48]. In some studies, the presence of stimulatory anti-β1AR-AAbs was associated with a three-fold increase in all-cause and cardiovascular mortality after adjustment for conventional risk factors [1, 26]. In addition, the presence of stimulatory anti-β1AR-AAbs in DCM patients was associated with a higher prevalence of ventricular premature contraction (VPCs; multiform premature ventricular beats or couplets) [26]. Nevertheless, the presence of stimulatory anti-β1AR-AAbs was not associated with higher risks of ventricular tachycardia (VT) [26]. It was reported that patients with anti-β1AR-AAbs higher than 10 units/ml had significantly worse survival rates compared with patients with lower values [49]. In a study of 104 idiopathic DCM patients, the presence of anti-β1AR-AAbs was found to be the strongest independent risk factor for multifocal VPCs, overall VT, and high-risk VT on a Holter ECG. However, no differences were found in the total number of ventricular and supra-ventricular premature beats between anti-β1AR-AAbs-positive and anti-β1AR-AAbs-negative patients [30]. In the same study, the anti-β1AR-AAbs-positive group had significantly more cases of sudden death, although overall cardiac-related mortality and prevalence of heart failure was similar compared with the anti-β1AR-AAbs-negative group [30].

Aso et al. investigated anti-β1AR-AAbs in 52 patients with chronic heart failure; 44 had no ischemic origin [49]. They reported a correlation between anti-β1AR-AAbs and cardiac sympathetic activity, observed by myocardial iodine-123 metaiodobenzylguanidine imaging [49].

Ischemic Cardiomyopathy

Although anti-β1AR-AAbs are more commonly found in DCM patients, they may be detected in approximately 10% of patients with ischemic cardiomyopathy (ICM) [30]. Other studies have reported a prevalence of 20%, all of

which are high activators of the β1-AR [18]. In a 10-year follow-up study of 40 patients with ICM (five positive for stimulatory anti-β1AR-AAbs), the presence of stimulatory anti-β1AR-AAbs was not associated with an increased risk for all-cause mortality and cardiovascular-related mortality, as in DCM patients [26]. Nevertheless, this study was too small to draw a definite conclusion regarding the prognostic importance of anti-β1AR-AAbs in ICM.

Chagas Heart Disease

Millions of people worldwide, mainly from Central and South America, are infected with the protozoan parasite *Trypanosoma cruzi*. Of those infected, 25–30% will develop chronic infections and cardiac involvement also known as Chagas heart disease (ChHD). In addition, 10% will die from severe myocardial dilatation, heart failure, or ventricular arrhythmias [50]. Several possible explanations for heart failure evolvement in ChHD were described: chronic parasitic infection, autoimmune-mediated cardiomyopathy, and microvascular dysfunction [50].

Histologically, parasites are usually not found in the heart, although parasitic DNA segments and parasitic proteins can be detected in some cases [51]. ChHD is characterized by elevated sera levels of anti-β1AR-AAbs and an anti-M2 muscarinic acetylcholine receptor. It has been suggested that these autoantibodies contribute to the pathogenesis. Interestingly, antibodies against the parasitic ribosomal protein P2β cross-react with the second extracellular loop of β1-AR, thus apparently increasing the risk for life-threatening ventricular arrhythmias [52]. Immunization of mice with the P2β protein resulted in ECG changes and increased heart rate due to agonistic activity of the autoreactive antibodies [51]. The degree of systolic dysfunction is highly predictive for early mortality. ChHD grading is determined according to electrocardiographic and echocardiographic findings [52]. Anti-β1AR-AAbs are present in about 30% of patients with ChHD [1], although according to early reports, prevalence may be as high as 50% [18]. Surprisingly, no association was found between the grade of ChHD, severity of contractile dysfunction, and measured circulating levels of anti-β1AR-AAbs [50]. Nevertheless, this study has quantified autoantibody concentrations but did not evaluate their function.

Anti-β1AR-AAbs-Directed Therapy

It appears that the presence of anti-β1AR-AAbs may contribute to heart disease progression and mark adverse prognosis in some patients [19], thus treatment directed against anti-β1AR-AAbs seems medically reasonable. Several therapeutic approaches have been reported with different effectiveness rates.

Intravenous Immunoglobulins

Studies have demonstrated that intravenous immunoglobulins (IVIG) are beneficial in DCM and have suggested that anti-idiotype properties of IVIG preparations and its ability to shorten the half-life of pathogenic antibodies was a major contributor to the presumed benefit in autoimmune DCM [31, 36]. In a randomized double-blinded study of 40 patients with symptomatic heart failure due to DCM or ICM, 20 patients were treated with IVIG. IVIG was associated with an increased ejection fraction, unobserved in the placebo-treated group, in addition to a greater improvement of quality of life [53]. Nevertheless, some studies reported no contractile benefit following IVIG in patients with heart failure or recent-onset DCM [35]. In a randomized control trial of 62 patients with new-onset DCM, 33 received IVIG. Both groups had an improved ejection fraction at 6 months follow-up [53]. Yet, IVIG infusion in DCM patients caused an increase rather than decrease of anti-β1AR-AAbs levels, indicating that IVIG does not neutralize anti-β1AR-AAbs and that its possible beneficial effect on certain heart diseases occurs due to a different mechanism [31].

Immunoadsorption

Immunoadsorption (IA) is a process where pathogenic autoantibodies are eliminated by an extracorporeal IgG adsorption system. IA was found to decrease the myocardial inflammatory process encountered in DCM [35]. Encouraging clinical results following the use of IA in eight DCM patients was first reported in 1996 by Wallukat et al. [33]. Schimke et al. evaluated the efficacy of selective IA in eight other patients with idiopathic dilated cardiomyopathy and reported, a year later, that decreased markers of oxidative stress and a significant increase in ejection fraction were found [54]. Jane-Wit et al. [17] found that DCM induction in mice following a passive transfer of anti-β1AR-AAbs was prevented due to anti-β1AR-AAbs-specific IA. In a prospective case-controlled study of 34 DCM patients with progressive heart failure, in candidates for heart transplantation, 17 received IA therapy for five consecutive days in addition to standardized therapy for heart failure. Subsequently, reduction of anti-β1AR-AAbs levels by a mean of 93.2% after 3 months was maintained after a year [36]. In the treated group, ejection fraction increased after 1 year from 22.3±3.3% to 37.9±7.9%, as well as the NYHA functional class. Moreover, left ventricular internal dimension in diastole and systole decreased significantly [36]. DCM patients not treated with IA had no significant

echocardiographic change on 1 year follow-up. Their levels of anti-β1AR-AAbs remained unchanged [36].

Staudt et al. suggested that IA in patients with DCM should focus on the elimination of the IgG-3 subclass [55]. Baba et al. evaluated the effects of selective IgG-3 IA on 18 patients with advanced heart failure and a left ventricular ejection fraction lower than 30%, who were sero-positive for anti-β1AR-AAbs and/or anti-M2 receptor, reporting that an increase of ejection fraction was significantly associated with treatment completion [56].

Specific IA for removal of anti-β1AR-AAbs was performed in eight patients with idiopathic DCM and was associated with an increased ejection fraction and decreased left ventricular internal dimension [33]. Specific IA can alleviate the need for an immunoglobulin substitute, commonly required, following non-specific IA. In addition, IA followed by administration of intravenous IgG in 22 DCM patients with systolic dysfunction (seven were positive for anti-β1AR-AAbs) caused an improvement in hemodynamic parameters and contractile function, regardless of the presence or absence of anti-β1AR-AAbs [34, 35]. It is therefore possible that IA benefited DCM patients in a way that does not involve just anti-β1AR-AAbs elimination, although it would have been expected that sero-positive patients would benefit more. Moreover, in this particular study, the administration of immunoglobulins served as a confounder, although there are reports as to the benefits of IA before substituting immunoglobulin [35]. Evidences for IA efficacy in a rabbit model of autoimmune dilated cardiomyopathy were demonstrated by Matsui et al. [57]. In conclusion, there is supporting evidence as to the benefit of IA in DCM patients, although it remains unclear how much of this benefit is attributable to the elimination of anti-β1AR-AAbs.

IA use in ChHD decreases the levels of autoantibodies reacting with β1-AR in the patient's sera. Therefore, IA might prove to be an effective treatment of ChHD, especially in cases of ventricular arrhythmias [52].

Plasma Exchange

An alternative to IA in the elimination of autoantibodies is plasma exchange (PEx), when the patient's plasma is replaced with a 4% albumin saline solution [58]. Review of the medical literature yielded a single case report of a DCM patient, positive for anti-β1AR-AAbs, treated with PEx and subsequent immunosupression. PEx resulted in a rapid reduction of autoantibodies levels and improved physical performances. Nevertheless, PEx had to be repeated 1 year later due to echocardiographic deterioration [59]. The disadvantages of PEx are: lack of selectivity, risks of bleeding, need for donor plasma or albumin substitution, increased risk of viral infections, and overall more complications than observed in IA.

β-adrenoreceptor Antagonists

Heart failure is commonly treated with β-adrenoreceptor antagonists, resulting in improved survival, improvement of ventricular functions, reversal of cardiac remodeling, and reduction of heart rate and blood pressure. Blockage of the molecular and cellular effects of anti-β1AR-AAbs on cardiomyocytes is another possible mechanism benefiting patients with contractile dysfunction [32]. Labetolol, metoprolol, and propanolol (but not bisoprolol or atenolol) were found to inhibit ERK cascade activation and subsequent cardiac hypertrophy and failure [23]. Treatment of 106 heart failure patients (due to DCM, ICM, and hypertensive heart disease) with metoprolol (in addition to conventional anti-heart-failure therapy) resulted in greater improvement of contractile function and reversal of remodeling in anti-β1AR-AAbs-positive patients [60]. β-blockers are associated with a decreased incidence of high-risk VT in anti-β1AR-AAbs-positive DCM patients (95% confidence interval 0.01 to 0.89; odds ratio, 0.11) [30], suggesting that they may decrease electrophysiological instability due to anti-β1AR-AAbs. Yoshikawa et al. [16] found that β-blockers prevented anti-β1AR-AAbs-induced apoptosis. In a trial of 82 patients with congestive heart failure (20 were sero-positive for anti-β1AR-AAbs), the effects of β-adrenoreceptor antagonists were evaluated. It was found that patients with anti-β1AR-AAbs responded better to β-blockers, increasing their ejection fraction, left ventricular end-diastolic and end-systolic dimension, in a more significant manner than patients without circulating anti-β1AR-AAbs [20]. Carvedilol appears to be more beneficial than metoprolol in patients with heart failure and anti-β1AR-AAbs [20]. Molecular investigation of anti-β1AR-AAbs-mediated cAMP increase was evaluated following addition of β-blockers. Nikolaev et al. [18] demonstrated that both β1-selective and non-selective antagonists decreased anti-β1AR-AAbs-mediated cAMP production. Nevertheless, the reduction was partial, 50% following alprenolol, 60% following bisoprolol, or up to 70% following carvedilol [18]. Interestingly, metoprolol was reported to significantly reduce the anti-β1AR-AAbs titer [60], although the mechanism remains unknown.

Miscellaneous

A novel anti-β1AR-AAbs-targeted therapy could be applied with direct targeting of the autoreactive Abs-producing B cells by induction of immune tolerance [1, 14]. In a rat model, when anti-β1AR-AAbs were induced, a prophylactic prescription of homologous cyclopeptide (for the second extracellular loop of β-1-AR), resulted in decreased anti-β1AR-AAbs levels, thus preventing DCM-like heart changes [1].

Another proposed pharmacological approach is oversaturation of pathogenic autoantibodies with receptor-homologous peptides such as sequences of the second extracellular loop of β-1-AR. The combined use of these peptides with β-blockers (bisoprolol) resulted in a full blockage of the anti-β1AR-AAbs-mediated cAMP increase, compared with a 60% reduction when bisoprolol was applied alone, indicating a synergistic effect of the two methods [18].

In an attempt to prevent anti-β1AR-AAbs-mediated apoptosis, several participating molecules can potentially be used: cAMP inhibitors, PKA inhibitors, and caspase-pathway inhibitors [16]. Also, future research might focus on the inhibition of p-38 mitogen-activated protein kinase activation, or cease PI3K-Akt signaling pathway inhibition [39]. Nevertheless, to date, there has been no clinical experience with the latter targeted approaches.

Summary and Future Prospects

Anti-β1AR-AAbs appear to contribute to the pathogenesis of dilated cardiomyopathy, heart failure, and Chagas disease. However, it does not seem to contribute to the development of valvular or hypertensive heart diseases [44]. The presence of anti-β1AR-AAbs seems to be associated with an adverse prognosis in some patients [61].

Currently, standardized screening methods for detecting anti-β1AR-AAbs are lacking [1], resulting in major discrepancies among studies as to the reported percentages of anti-β1AR-AAbs-positive patients. Recently, a novel method of detecting functionally active anti-β1AR-AAbs by evaluating receptor-mediated signaling (by measuring cAMP by fluorescence-resonance energy transfer) was proposed. It was reported that the new method has a tenfold higher sensitivity compared with conventional radioimmunoassay [18].

The type of the allosteric regulation induced by anti-β1AR-AAbs should be investigated for its possible influence on the pathogenesis and natural history of heart disease. In addition, the prognostic importance of anti-β1AR-AAbs should also be further investigated.

Although there is supporting evidence regarding the role of anti-β1AR-AAbs in various cardiac diseases in humans, a cause and effect relationship is difficult to establish. It appears that some DCM patients with circulating stimulatory anti-β1AR-AAbs are at an especially higher risk for adverse outcome and should probably receive anti-β1AR-AAbs-directed therapy. Anti-β1AR-AAbs-targeted therapy might provide hope for refractory DCM cases. Further research is necessary in order to evaluate patient characteristics to ascertain who will benefit the most from anti- anti-β1AR-AAbs therapy, in addition to evaluating the possible synergistic effects of different therapeutic approaches. Moreover, further efforts should be focused on identification and evaluation of the role of other cardio-pathogenic autoantibodies in autoimmune-mediated heart diseases.

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