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ADVANCES IN HEART FAILURE

β_1-Adrenoreceptor Autoantibodies in Heart Failure

Physiology and Therapeutic Implications

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ABSTRACT: Antibodies that activate the β_1-AR (β_1-adrenoreceptor) can induce heart failure in animal models. These antibodies are often found in patients with heart failure secondary to varying etiologies. Their binding to the β_1 receptor leads to prolonged receptor activation with subsequent induction of cellular dysfunction, apoptosis, and arrhythmias. β-blocker therapy while highly effective for heart failure, may not be sufficient treatment for patients who have β_1 receptor autoantibodies. Removal of these autoantibodies by immunoadsorption has been shown to improve heart failure in small studies. However, immunoadsorption is costly, time consuming, and carries potential risks. An alternative to immunoadsorption is neutralization of autoantibodies through the intravenous application of small soluble molecules, such as peptides or aptamers, which specifically target and neutralize β_1-AR autoantibodies. Peptides may induce immunogenicity. Animal as well as early phase human studies with aptamers have not shown safety concerns to date and have demonstrated effectiveness in reducing autoantibody levels. Novel aptamers have the potential advantage of having a wide spectrum of action, neutralizing a variety of known circulating G-protein coupled receptor autoantibodies. These aptamers, therefore, have the potential to be novel therapeutic option for patients with heart failure who have positive for β_1-AR autoantibodies. However, clinical outcomes trials are needed to assess the clinical utility of this novel approach to treat heart failure.

Key Words: adrenergic ■ autoantibodies ■ cardiomyopathies ■ heart failure ■ peptides ■ receptors

Heart failure (HF) is highly prevalent and associated with a high risk of mortality and hospitalization, as well as poor quality of life. While ischemic etiology of HF and reduced ejection fraction may be present in the majority of patients, up to a third of these patients have nonischemic HF.[1] Depending on the method of detection and type of antibodies being studied, cardiac autoantibodies are detected in 10% to 30% of patients with ischemic and 20% to 95% in patients with a nonischemic HF.[2,3] Animal experiments suggest that autoantibodies are associated with the development of HF after ischemic events.[4] Some of these antibodies activate the β_1-AR (β_1-adrenoreceptor). Prolonged activation of β_1-AR by antibodies can result in cellular dysfunction, apoptosis, and arrhythmias. Early experience has suggested that removing antibodies might improve cardiac function. The aim of this review is to discuss the potential relevance of antibodies against β_1-AR in patients with HF as well as novel therapies targeted at autoantibodies to these receptors.[2,3]

CARDIAC AUTOANTIBODIES

The most frequently detected cardiac autoantibodies are those against myosin, troponin I, β_1-AR, muscarinic receptors, anti-Na-K-ATPase, anti-endothelin A receptor, and anti-AT-1 receptor.[5] Interestingly, several arrhythmogenic autoantibodies targeting specific calcium, potassium, or sodium channels in the heart have been recently identified, but their role in HF remains elusive.[6,7] For the majority of these autoantibodies, their role in development or progression of HF is uncertain.[2,5,8] However, a possible role for autoimmunity in the causation or progression of idiopathic dilated cardiomyopathy (DCM) has

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Nonstandard Abbreviations and Acronyms

AR	adrenoreceptor
DCM	dilated cardiomyopathy
HR	heart rate

been suggested. Experimentally, this has been corroborated by immunizing animals to produce antibodies to the β_1-AR and demonstrating development of DCM.[5] In humans relatives of DCM patients, anti-cardiac autoantibodies were recognized in one study as an independent predictor for HF development within 5 years.[9]

Although present in patients with HF and reduced ejection fraction, β_1-AR antibodies are also found in healthy subjects which has led to uncertainty about their pathophysiological significance.[3,10] In healthy individuals, it is thought that these antibodies may be nonfunctional and target similar epitopes found on microbes, that is, cross-react with reagents designed to detect β_1-AR.[2] Interestingly, β_1-AR autoantibody were found in as many as 90% of patients who required implantation of a left ventricular assist device, further suggesting their possible role in the progression of HF.[3,10] The successful removal of these antibodies with a β_1-AR autoantibody-specific adsorber column and subsequent long-term benefits underscores the potential impact of β_1-AR autoantibodies on the pathogenesis of HF.[3] A summary of the prevalence of autoantibodies with potential cardiac effects in healthy people and different HFcohorts is shown in Table 1.[11] Among the many cardiac autoantibodies found in HF, data on the potential role in causation, progression, and treatment of β_1-autoantibodies is the most consistent.

β_1-ADRENORECEPTOR AUTOANTIBODIES IN HF

It is hypothesized that the development of pathogenic autoantibodies occurs through autoimmunization. This is consistent with the alterations in humoral and cellular immunity observed in HF. Autoimmunization may occur through antigen mimicry (eg, Chagas disease) or by injury-induced release of immunity-hidden autoantigens (eg, viral or ischemic damage).[12,13] Persistent activation of the β_1-AR by catecholamines has several negative effects including ischemia caused by increased heart rate and contractility, calcium overload with mitochondrial dysfunction, oxidative stress, metabolic alterations, and vasoconstriction (Figure 1).[14] Hyperadrenergic state in HF affects signal-transducing homeostasis through downregulation of adrenergic receptors and promotes cardiac remodeling. This process can be slowed or reversed by β-blockers, which prevent binding of agonists but induce upregulation of the receptors.[15] Thus, theoretically, β-blocker might contribute to the pathogenic effect of the β_1-AR autoantibodies by upregulating receptors.

β_1-AR autoantibodies stabilizes the receptor in its active form, inducing prolonged activation similar to cathecholamines (Figure 2).[16] This agonist effect is further enhanced by the lack of counter-regulatory downregulation of receptors, which usually occurs during overstimulation by agonists.[17] This modulatory effect of autoantibodies may, therefore, require additional therapy besides β-blockers. In the short-term, β_1-AR autoantibodies increase the beating frequency and the duration of the action potential, L-type Ca^{2+} current and contractility, in vitro.[18] In the long-term, β_1-AR autoantibodies induce apoptosis in immunized mice, similar to that caused by isoproterenol.[19] Moreover T-cell activation via β_1-AR autoantibodies causes IL-6 release,[20] which sustains the vicious cycle able. Although the mechanism of initiation of antibody formation is unknown, activated toll-like receptor 9 might explain the link that connects innate and adaptive immunity.[21,22]

In DCM, β_1-AR autoantibody titers are associated with the risk of ventricular tachycardia and sudden death.[23] Störk et al have also shown that β_1-AR antibody titer predicts all-cause and cardiac mortality among patients with idiopathic cardiomyopathy.[24]

In summary, the pathological effect of the β_1-AR autoantibodies on cells is caused by prolonged activation of β_1-adreno receptors by stabilizing them in their active form. This activates intracellular signaling molecules similar to those in hyperadrenergic state. This overstimulation induces apoptosis and fibrosis, which may lead to a new-onset HF and its progression. These patients have a higher risk of ventricular arrhythmias and a sudden death.

DIAGNOSTIC OF β_1-ADRENORECEPTOR AUTOANTIBODIES

For β_1-AR autoantibodies to be a target for therapy, a standardized, validated, affordable, widely available diagnostic test will be needed. No such test is

Table 1. Prevalence of Cardio-Pathogenic Autoantibodies in Healthy Subjects and Patients With Cardiomyopathy

	β_1-AABs (%)	Muscarin Receptor Type 2–AABs (%)	c-Myosin AABs (%)	c-Tn AABs (%)
Healthy subjects	<19	<17	<12.5	<13
Ischemic cardiomyopathy	10–55	50–62	4–30	18
Dilated cardiomyopathy	26–95	15–50	20–66	15–30
Chagas cardiomyopathy	30–98	26–100	11–38	40
Peripartum cardiomyopathy	60–100	46	24	26

AABs indicates autoantibodies; β_1, β_1-adrenergic receptor; muscarin receptor type 2, muscarinic 2 receptor; c-myosin, cardiac myosin; and cTn, cardiac troponin.

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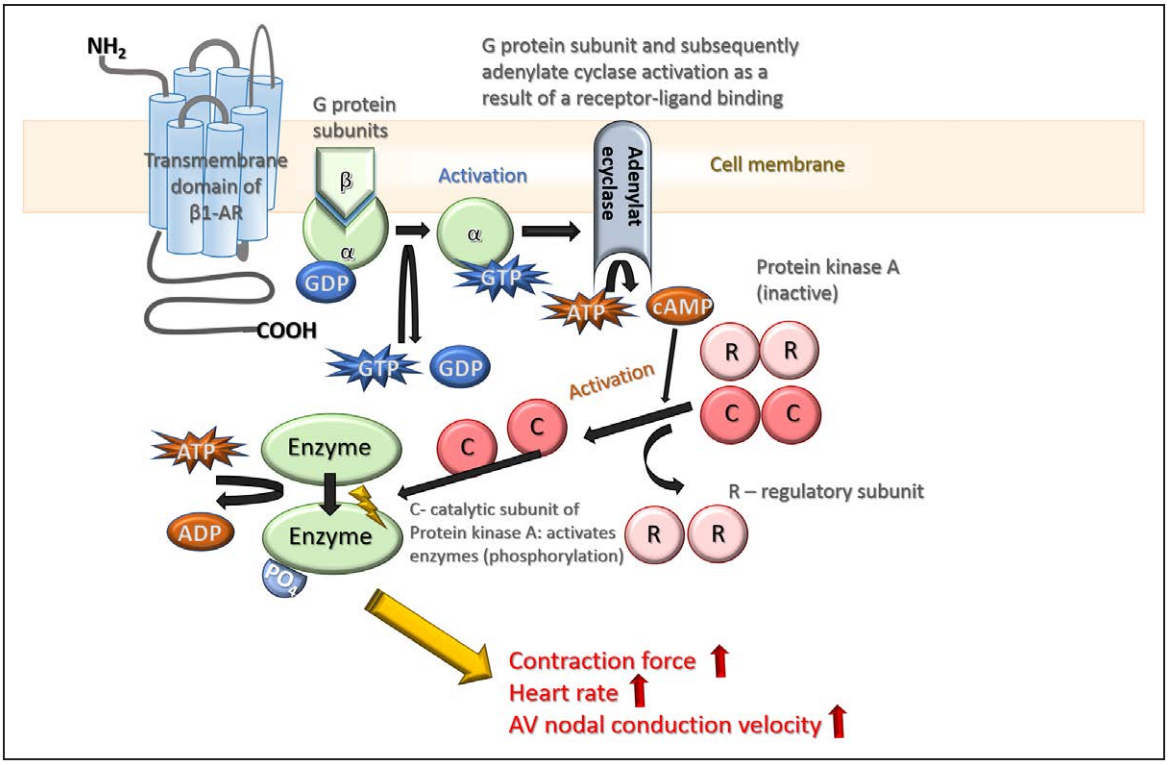

Figure 1. Schematic illustration of a G protein-coupled receptor with signal transduction cascade of the β_1-AR (β_1 adrenoreceptor).

The blue cylinders represent the transmembrane domain of the β_1-AR. Lines that connect the cylinders are remaining parts of receptor forming intra and extra-cellular loops. α and β are G protein subunits. Four red circles filled with either R or C represent altogether the inactive protein kinase A, whereas 2 of them filled with C note protein kinase after activation of the β_1-AR. Two circles with R are regulatory subunits of protein kinase. Enzyme labeled oval field represents different enzymes activated by protein kinase A, inducing inotropic effects. ADP indicates adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; and GTP, guanosine triphosphate.

available yet. The tests described to date are depended on either (1) the functional effects of the autoantibodies, using living cells which are the so-called bioassays or (2) simple binding, exploiting solid-phase binding technology, such as an ELISA. There are 2 problems with existing approaches.[25,26] First, the functional autoantibodies of interest bind to receptors in their native state (as found in assays using living cells) and not to denatured proteins such as those used in solid-phase based assays, even when these assays are based on cell-proteins.[25] This and the lack of proper analytical control measurements has produced conflicting data about the prevalence and functional significance of autoantibodies in healthy individuals.[27–30] A particular concern about solid-phase based assays (eg, ELISA) is that immunoglobulins (IgG, antibodies) from patients suffering from autoimmune diseases bind to uncoated (antigen free) enzyme-linked immunosorbent assay wells, as well as to those coated with antigen.[31–33] This seems to be a problem that is specific for human samples. With autoantibodies induced in animals, the ELISAs function well.[34] With autoantibodies generated in immunized animals, not only the ELISAs function well, same is true for immunofluorescence techniques.[35] This raises questions about the sensitivity and specificity of such tests for the use with samples of human origin. Li et al[36] compared ELISA technology with new cell-based bioassays based on either cAMP formation after β2 AR activation or β-arrestin recruitment after M3R (muscarinic 3 receptor) activation not being able to see a correlation.

Second, functional assays often measure beating frequency in spontaneously beating neonatal rat cardiomyocytes.[3,37,38] This requires freshly prepared cells and interpretation of the assay is quite skilled and requires training; hence the test can only be conducted in specialized laboratories.[25] Nevertheless, functional assays have been developed which demonstrate the reproducibility, sensitivity, and specificity required of other commonly used tests.[39] An alternative test which uses fluorescence related to cAMP production in a cellular assay, is also being developed. Both of these functional tests (rat cardiomyocytes and fluorescence resonance energy transfer) are time consuming, and a single operator can manually analyze only 10 to 15 samples per day.[25] If these assays are to become widely used, they will have to be automated and attempts are currently underway to do this (Table 2).[40]

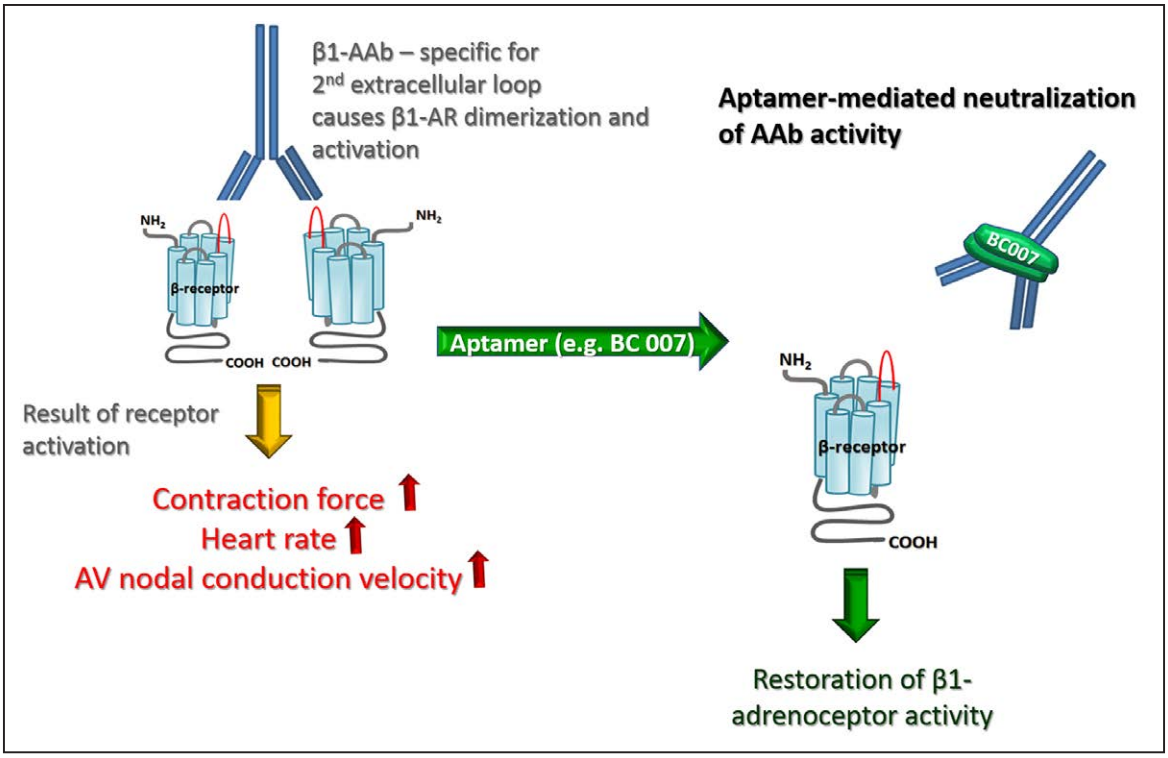

Figure 2. Schematic illustration of autoantibody binding to second extracellular loop of β_1-AR (β_1 adrenoreceptor). **Left**, The blue cylinders represent the transmembrane domain of the G protein-binding β_1-AR. Lines that connect the columns are remaining parts of receptor forming intra and extra-cellular loops. Lambda shaped figure represents autoantibody binding to second loop of 2 G protein-coupled β_1-ARs, which changes their conformation and activates them. **Right**, When given an autoantibody neutralizing aptamer BC 007 (specific aptamer), the binding of the autoantibody to the receptor is disabled as the aptamer is bound to the antibody. AAb indicates autoantibodies.

ELIMINATION OR NEUTRALIZATION OF β_1 ANTIBODIES IMPROVES HF

Proof of Concept Immunoadsorption

Because of its therapeutic application in other autoimmune diseases, immunoadsorption has been suggested as a possible treatment for patients with anti-cardiac antibodies.[41] Immunoadsorption clears molecules from the plasma by using binding column specific for themolecule(s) in question. The need to establish vascular access and use a plasma separator, binding columns, anticoagulation, and fluid replenishment, rendersimmunoadsorption demanding to perform.[42] In most studies, immunoadsorption was performed over 5 consecutive days.[37,43–45] In some studies, intravenous immunoglobulin substitution was performed after immunoadsorption to prevent infectious complications that might arise from depletion of circulating IgG. Columns specific for immunoglobulin G_3 subgroup antibodies or nonspecific with or without intravenous Ig substitution have been used.[37,44,46]

The first study in patients with DCM was performed in 1996.[47] Altogether, 12 studies have been performed in DCM, 6 using nonselective and 5 a selective approach, and 1 comparing both. The studies included between 8 and 108 patients. Effectiveness of therapy was assessed over a period of between 3 and 12 months. Improvement of ejection fraction was shown in 10, improved functional class in 7, and reduced natriuretic peptides in 5 (Table 3).[3,37,38,43–51] Reinthaler et al[52] suggested that initial responders to therapy, who subsequently had a recurrence of autoantibodies, seemed to benefit from repeat immunoadsorption. All of these studies were small and with one exception were not randomized or blinded. The only randomized trial included only 18 patients with DCM with ejection fraction <30%. Treated patients had improvement in cardiac index, stroke volume, and systemic vascular resistance after 3 months.[49]

Table 2. Diagnostic Tests for Detection of Functional β_1-Adrenoreceptor Autoantibodies

Test	Applicability	Reproducibility	Time Consumption	Validity
ELISA	+++	+	+	+
Spontaneous beating cardiomyocytes functional test	+	++	+++	+++
FRET	+	++	+++	unknown

Table represents main tests being used to detect functional β_1 adrenoreceptor autoantibodies, and their applicability, reproducibility, time consumption, and validity expressed on scale from + to +++.[25–40] FRET indicates fluorescence resonance energy transfer.

Table 3. Immunoadsorbtion of β_1-AR Antibody in Heart Failure

Reference	Intervention	Study Design	Follow-Up	Results
Wallukat et al[47]	IA+IVIg	Case series (n=8)	NA	7/8 patients improved NYHA class
Dörffel et al[37]	IA+IVIg	Case series (n=9)	6d and 3y	Improved hemodynamics; no change in LVEF 5/9 patients alive; improved EF
Müller et al[38]	IA	Prospective case-control (n=34)	1 y	Improved EF; decreased oxidative stress markers
Felix et al[49]	IA+IVIg	RCT (n=18)	3 mo	Improved LVEF and NYHA
Dandel et al[3]	IA vs sel IA	Retrospective case series (n=108)	5.3–14.7 y	Improved LVEF and transplant/VAD-free survival in patients with Ab
Pokrovsky et al[45]	IA	Case-control (n=16)	6 mo	Improvement of NYHA, BNP, and 6MWT regardless of β1 Ab existence
Staudt et al[43]	Sel IA+IVIg vs no IA	Case-control (n=18)	3 mo	Improved LVEF and NT-proBNP
Baba et al[50]	Sel IA	Case series (n=18)	3 mo	Improved LVEF, 6MWT, BNP, inpatient with removal of cardio depressant Abs
Staudt et al[48]	Sel IA+IVIg	Case series (n=103)	6 mo	Improved LVEF and NYHA
Nagatomo et al[46]	Sel IA	Case series (n=16)	3 mo	Improvement of LVEF, NYHA, and 6MWT
Yoshikawa et al[51]	Sel IA	Randomized trial (n=40) 1:1 IA vs delay group	12 mo	Improvement of LVEF, NYHA, VO_2, NT-proBNP, QoL, cardiothoracic ratio ratio
Ohlow et al[44]	Sel IA+IVIg	Retrospective case series (n=93)	12 mo	Improvement in QoL, NYHA, LVEF, EDD, Nt-proBNP; 48% responders

Ab indicates antibodies; β1-AR, β1 adrenoreceptor; BNP, B-type natriuretic peptide; EDD, end diastolic diameter; EF, ejection fraction; IA, immunoadsorbtion; IVIg, Ig substitution; LVEF, left ventricular ejection fraction; MWT, minute walk test; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life; RCT, randomized controlled trial; Sel IA, selective IA; VAD, ventricular assist device; and VO_2, oxygen uptake.

Autoantibody Neutralization Options

Neutralization of autoantibodies can be achieved using (1) small peptides or (2) aptamers that bind specifically to the target autoantibodies.[53]

Peptides for Autoantibody Neutralization

The use of peptides for autoimmune therapy may follow the exploitation of peptide antigens for the induction of regulatory cells for treatment of autoimmune diseases.[54] Some peptides also induce cytotoxic $CD8^+$ T-cell response, described as a double-edged sword.[55] The use of the epitope peptide sequences for competition with the receptors for the autoantibodies is another approach that is being studied in a range of autoimmune diseases, including rheumatoid arthritis, myasthenia gravis, and Graves' disease and rheumatoid arthritis.[56,57]

Peptides for β_1-AR Autoantibody Neutralization

A cyclic peptide lead to antibody neutralization in rats immunized with a protein similar to second extracellular loop of β_1-AR.[58] Rats immunized with such protein develop a DCM.[59] This peptide use suggest that it could prevent, stop, and even reverse the damage done by immunization. This was explained through its scavenging effect on circulating antibodies and its depletion effect on memory B-cells which produce these antibodies.[58] One peptide, cyclic peptide (JNJ-54452840), has been investigated in a phase I study in healthy humans and in patients with DCM.[60,61] In a phase II double-blind, parallel-group, controlled trial, patients were randomly assigned to 20, 80, and 160 mg of cyclic peptide, or placebo, given for 6 months. Cyclic peptide had no effect on left ventricular ejection fraction, natriuretic peptides, or 6-minute walk distance. The most common adverse event among treated groups was nasopharyngitis. Weakness of the study included using nonvalidated bioassay for antibody detection and high rate of treatment discontinuation.[62]

Aptamers

General Remarks About Aptamers

Aptamers are oligonucleotides made of single- or double-stranded RNA or DNA sequences, with a high affinity for their targets. The main advantages of aptamers over peptides are their low toxicity and low risk of immunogenicity.[63] Hypersensitivity has not been observed with this molecule class and especially not with the nonmodified nucleic acids. In cases where immunogenic reactions had been seen, this was due to modifications of the oligonucleotide substance (eg, pegylation).[64] Aptamers are easier to synthesize and modify than peptides. They are stable when heated and can be administered intravenously or subcutaneously.[65,66] An aptamer is currently approved for treatment of macular degeneration and many more are under investigation.[67,68] One challenge is how to prolong the half-life of aptamers in blood. They are distributed to nontargeted tissues and are renally filtered and susceptible to degradation by nucleases. Nuclease degradation can be prevented by chemical modification and renal clearance prevented by pegylation or adding cholesterol to the aptamer.[65]

First aptamers specific for autoantibodies were studied in 1992, where Tsai et al[69] selected an RNA aptamer which functioned as a specific inhibitor of a selected antibody-antigen interaction. This was followed by a variety of aptamer selection, for example, an RNA aptamer

which used serum from a patient with systemic lupus erythematosus[70] or the isolation of a nuclease-resistant decoy RNA that can protect human acetylcholine receptors from myasthenic antibodies.[71]

Aptamers for β1-AR Autoantibody Neutralization—In Vitro Studies

A first aptamer specific for β1-AR antibodies, aptamer 110, neutralized the human autoantibodies in vitro. Rat cardiomyocytes were incubated with each of human serum containing autoantibodies to the β1-AR antibody, aptamer 110, or a mixture of both.[72] The high affinity of aptamer 110 for the β1-AR antibody could limit its therapeutic potential as multiple antibodies can occur in the same disease as to be seen in DCM where the autoantibody against the β1-AR[73] but also the muscarinic M2 receptor has been described.[74] With BC007 an aptamer has been described which showed affinity for multiple G protein-coupled receptor autoantibodies, including β1 first and second loop, α1, angiotensin receptor type 1, endothelin A receptor, and muscarinic receptor type 2 under in vitro conditions.[75–77] This was replicated in vivo as well.[78] A truncated version of aptamer 110 bound to an immunoadsorption column cleared serum of antibodies specific for the second extracellular loop of β1 receptor, whereas no Ig or proteins were bound to column when a control solution containing nonspecific Ig was used.[75]

Aptamers for β1-AR Autoantibody Neutralization—In Vivo Studies

Aptamers can also be used to clear blood of β1-AR autoantibodies by in vivo extracorporeal immunoadsorption. Immunoadsorption column bound with truncated version of aptamer 110 was used to treat spontaneous hypertensive rats positive for β1 (II) AR autoantibody. The immunoadsorption was performed in 2 rats once daily for 4 consecutive days. The control rat was treated with a control column. Rats treated with the specific aptamer columns had a significantly lower β1 (II) AR antibody titer. Type 2 antimuscarinic antibodies titer remained unchanged compared with control.[75] Haberland et al[72] demonstrated in vivo neutralization of β1-AR autoantibodies in rats using either aptamer 110 or BC007.[76] Aptamer 110 was given as an intravenous bolus of 2 mg/kg of body weight, followed by infusion of same amount over 20 minutes. The treatment was repeated weekly on 5 occasions. Antibody titer was expressed as an absolute change in beating frequency of cardiomyocytes in a minute. Significant reduction in antibody titer was noticed after the first measurement and titers remained low in blood samples drawn 21 weeks after last dose.[79] BC007 has also been tested for in vivo neutralization. Rats receiving aptamer BC007 had a significant reduction in β1-AR autoantibody after the first dose of treatment which remained low until the end of the study 120 days later. Antibody titer was measured using a spontaneous beating neonatal rat cardiomyocyte assay (Table 4).[76]

Safety and Tolerability of Aptamer Treatment

In general, the safety and tolerability are acceptable with this molecule class.[64] With BC007, a phase I randomized trial was recently performed. Healthy volunteers aged 18 to 45 were divided in 3 groups of 8 subjects and treated with 15, 50, or 150 mg of aptamer, placebo controlled (3:1). An additional cohort of 8 elderly healthy volunteers, aged 55 to 70 years, were assigned to placebo or 150 mg of aptamer. In a further open-label investigation, 7 groups of 6 elderly healthy volunteers, aged 55 to 75 years, with evidence of G protein-coupled receptor autoantibodies, were exposed to 50, 150, 300, 450, 750, 1350, and 1900 mg of aptamer. Drug was applied as

Table 4. Results of Preclinical Studies on Aptamers

Reference	Intervention	Study Design	Follow-Up	Result
Haberland[72]	Aptamer neutralization of human Ab	In vitro rat cardiomyocytes	NA	Aptamer inhibits apoptosis, and chronotropic effects of Ab
Wallukat[75]	Apheresis-4 consecutive days	In vivo SHR proof of principle (N=4)	Ab levels remained low for 60 days	Reduction of β1 antibodies
Haberland[79]	Intravenous bolus+infusion, 5 times in weekly intervals	In vivo SHR case-control (N=10)	Ab levels remained low for 21 weeks	Reduction of β1 antibodies with no substantial return. Decrease in wall thickness
Wallukat[76]	1. BC007 aptamer neutralization of human Ab.	In vitro rat cardiomyocytes	NA	In vitro reduction of concentration of multiple antibodies
	2. BC007 neutralization of sera of IA responders			
	3. BC007 IV bolus +infusion, 5 times weekly	In vivo SHR	Ab levels remained low until the end of the study (120 days)	In vivo reduction of Ab without substantial return
Haberland[77]	BC007 aptamer neutralization of Ab in serum	In vitro rat cardiomyocytes	NA	Reduction of multiple antibodies
	BC007 aptamer neutralization of Ab using column			Neutralization of Ab through aptamer columns

Table represents main studies on aptamer with interventions being used, study design, follow-up time, and results. Ab indicates antibodies; BC007, specific aptamer; IA, immunoadsorbtion; IV, intravenous; NA, not applicable; and SHR, spontaneously hypertensive rats.

an intravenous infusion over 20 minutes for doses up to 150 mg. Lower doses were administered as a combination of bolus plus infusion, whereas higher doses were administered by infusion (NTC02955420). No clinically significant adverse events were observed. Transient prolongation of aPTT was noticed in groups treated with 300 mg or more of aptamer, which lasted until the end of the infusion. Neutralization of autoantibodies at even one month after application was achieved in 2/6 at 300 mg, which increased up to 6/6 in the cohort treated with 1900 mg BC007.[78,80] Analysis of urine and serum showed that the aptamer degraded rapidly into its final products, such as β-aminoisobutyric acid and uric acid. Uric acid levels were increased only briefly with high-dose treatment (1300 and 1900 mg). The 2 products may be useful in tracking the metabolism of the drug.[81] According to the sponsor, BC007 is currently under investigation for persistence of β_1-AR autoantibody removal in autoantibody-positive HF patients in phase IIa of clinical testing.

Conclusions

There is strong evidence that autoantibodies can cause or lead to progression of HF. Available data on functionally active autoantibodies against the β_1 adrenoreceptor is the most consistent. Removal of autoantibodies via immunoadsorption has been shown to be of therapeutic benefit. Immunoadsorption is relatively expensive and logistically difficult to implement. The direct neutralization of these autoantibodies in future may mitigate these concerns. Application of peptide epitope sequences with the receptors for the autoantibodies have so far not been shown to be advantageous. On the contrary, aptamers have shown that they can neutralize G-protein-coupled autoantibodies in vivo in humans. Aptamers are not expected to have immunogenicity potential. Human trials for peptides and aptamers are at the beginning phases, and further research is needed.

ARTICLE INFORMATION

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Disclosures

Drs Düngen, Felix, Pieske, Voors, McMurray, and Butler all consultants to Berlin Cures. They are all members of the scientific steering committee and have supported uncompensated the establishment of the study protocol for clinical phase 2 trial. This trial is currently ongoing. The other authors report no conflicts.

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