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VASODILATORS AND LOW DOSE ACETYLSALYCILIC ACID ARE ASSOCIATED WITH A LOWER INCIDENCE OF DISTINCT PRIMARY MYOCARDIAL DISEASE MANIFESTATIONS IN SYSTEMIC SCLEROSIS: Results of the DeSScipher inception cohort study

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ABSTRACT

Objectives

To investigate the influence of vasodilator drugs on the occurrence of features depending on myocardial ischemia/fibrosis

(ventricular arrhythmias, Q waves, cardiac blocks, pacemaker implantation, left ventricular ejection fraction -LVEF-<55% and/or congestive heart failure and sudden cardiac death) in Systemic Sclerosis (SSc).

Methods

Six hundred and 1 SSc patients were enrolled from December 1st, 2012 to November 30th, 2015 and had a second visit 0.5-4 years apart. 153 received no vasodilators; 448 received vasodilator therapy, (i.e. Calcium Channel Blockers and/or Angiotensin Converting Enzyme inhibitors or Angiotensin II receptor blockers or combinations of them), 89 of them being also treated with either endothelin receptor antagonists or PDE5 inhibitors or prostanoids. Associations between the occurrence of myocardial disease manifestations and any demographic, disease and therapeutic aspect were investigated by Cox regression analysis. A Cox frailty survival model with centre of enrollment as a random effect was performed.

Results

During 914 patient/follow-up years, 12 ventricular arrhythmias, 5 Q waves, 40 cardiac blocks, 6 pacemaker implantations, 19 reduced LVEF and/or CHF occurred. In multivariate Cox regression analysis, vasodilator therapy was associated with a lower incidence of ventricular arrhythmias (p=0.03); low dose acetylsalycilic acid (ASA) with a lower incidence of cardiac blocks and/or Q waves and/or pacemaker implantation (p=0.02), active disease with a higher incidence of LVEF<55% and/or CHF and cardiac blocks and/or Q waves and/or pacemaker implantation (p=0.05).

Conclusions

The present study might suggest a preventative effect on the occurrence of distinct myocardial manifestations by vasodilator therapy and low dose ASA.

Keywords: primary myocardial disease in scleroderma, preventative role of vasodilator therapy.

INTRODUCTION

Myocardial disease occurring in patients with Systemic Sclerosis (SSc) is classically subdivided into primary and secondary, depending the absence or, respectively, coexistence of pulmonary and/or renal involvement.[1-3]

Primary myocardial disease is morphologically characterized by vasculopathy of small arteries and biventricular patchy myocardial fibrosis which presents a strong association with contraction band necrosis, suggesting the implication of ischemia-reperfusion events i.e. a myocardial Raynaud's phenomenon (RP).[4] In this regard, short term trials and retrospective observational studies have underlined a beneficial effect of calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEinh) on cardiac vascularization and function.[5-11]

By now, the role of vasodilator agents in the prevention of primary myocardial disease in SSc has not yet been clarified. In order to define the management of SSc, a project named DeSScipher (To decipher the optimal treatment of SSc) was submitted to and funded by the European Community (FP7- HEALTH n°305495). Here, we report the results of the subproject devoted to investigate the influence of vasodilator drugs on the occurrence of primary myocardial complications, specifically those associated with a poor prognosis i.e. ventricular arrhythmias, Q waves , cardiac blocks , pacemaker implantation , reduced left ventricular ejection fraction (LVEF), congestive heart failure (CHF) and sudden cardiac death.[1-3,12-14]

METHODS

Patients and study design

Patients fulfilling the ACR/EULAR criteria for SSc,[15] consecutively admitted to 20 DeSScipher-EUSTAR centres from December 1st, 2012 to November 30th, 2015, were enrolled, according to local ethical requirements.

Patients with the following characteristics were excluded: significant pulmonary parenchymal (forced vital capacity and/or diffusing lung capacity for CO < 70%) or vascular involvement (estimated systolic pulmonary arterial pressure > 40 mmHg), intestinal involvement (malabsorption syndrome or paralytic ileus or renal involvement (serum creatinine level >1.2 mg/dl and/or dialysis or previous scleroderma renal crisis) or

any sign/symptom/ electrocardiographic (ECG) finding of myocardial disease, basal pulmonary rales and/or leg edema indicative of congestive heart failure.

Patients enrolled in the study were investigated according to the DeSScipher protocol, shared by all participating centres. In particular, they were assessed for the items listed in the European Scleroderma Trials and Research group (EUSTAR) protocol,[16] including European Scleroderma Study Group (EScSG) activity criteria.[17] Moreover, as far as myocardial disease is concerned, each patient was examined at baseline by means of medical history, clinical examination, ECG, Holter ECG and B-mode echocardiography at baseline, and was reassessed every 3 months with respect to medical history, clinical examination, and ECG, and every 6 months by Holter ECG and B-mode echocardiography until the end of each follow-up-year. According to local policies, patients had to undergo either standard vasodilator therapy i.e. CCB such as nifedipine up to 60 mg/qd or comparable doses of other drugs of the same class and/or ACEinh such as captopril up to 100 mg/qd, or no vasodilator therapy. Two hundred and 50 patients per arm had to be enrolled. Despite the strictly defined entry criteria, 2 major protocol deviations occurred. As far as treatment is concerned, some patients with baseline myocardial disease were enrolled. As far as treatment is concerned, 63 patients undergoing AgIIrb±CCB treatment were enrolled.Because of the influence on the same pathophysiologic pathway, they were considered in the same class of ACEinh and included in the arm of those treated with CCB and/or ACEinh, with the whole group being referred to as standard vasodilator therapy. Moreover, some patients treated with targeted vasodilator drugs (i.e. prostanoids or endothelin receptor antagonists or phosphodiesterase type 5 inhibitors), were enrolled. Out of them, those undergoing standard vasodilator therapy were included in the same arm which was referred to as vasodilator therapy; those treated with targeted vasodilator drugs only were excluded because of the intermittent drug regimen in most of them. The role of other features potentially influencing the occurrence of cardiac disease during follow-up was also investigated i.e. diffuse subset, disease activity, digital ulcers, traditional risk factors such as sex, cigarette smoking, systemic arterial hypertension, hypercholesterolemia and drugs including ongoing corticosteroids ± immunosuppressive therapy and low dose acetylsalycilic acid (ASA) (≤325 mg daily).[1-3,18-21]

Follow-up and outcome measures

The new occurrence of ventricular arrhythmias as manifestations indicative of myocardial ischemia, that of Q waves and/or cardiac blocks and/or pacemaker implantation as

manifestations indicative of myocardial fibrosis or a therapeutic intervention promoted by it, and that of LVEF<55% and/or CHF, as manifestations of evolved disease, were investigated.[1-4]

Finally, the incidence of withdrawal from treatment was used as safety endpoint.

Statistical analysis

StataMP 13, IBM SPSS 24.0 and MedCalc 11.3 for Windows software were used for statistical analyses. Continuous data were expressed as means and standard deviations (SD) and compared by t student test. The predictivity of myocardial disease occurrence by each distinct feature was assessed by Cox proportional hazard regression models. The number of covariates to be included in the multivariate model was defined by using a ratio of cases per covariate in the size of 10.[24] Moreover, in order to address the potential influence of different therapeutic strategies by clinician from different centres, we carried out a Cox frailty survival model with centre of enrollment as random effect.[25] Statistical significance was set at $P < 0.05$.

RESULTS

Patients

From December 1st, 2012 to November 30th, 2015, a total of 654 SSc patients, with a mean age of 56±13 years a disease duration from the first non-RP manifestation ranging from 0.5 to 61 years (mean 10±9 SD), were enrolled in the study and followed-up for at least six months.

One hundred and 53 patients did not undergo any vasodilator; 448 were prescribed vasodilators including 89 treated with either prostanoids and/or endothelin receptor antagonists and/or phosphodiesterase inhibitors. The 43 patients treated only with targeted vasodilators were excluded.

Table 1 shows the demographic, clinical, serological and therapeutic features as assessed at enrollment and during follow-up as far as the drug regimen is concerned, in the remaining 601 patients subdivided according to the therapeutic subgroup. Given the presence of missed items, the prevalence of each feature has been calculated among patients in whom it had been underlined. Hypercholesterolemia was noticed in few patients; no data were available for statin use.

With respect to patients undergoing no vasodilators, those treated with vasodilator therapy resulted to be more frequently aged ≥50 years (p=0.005), affected by systemic arterial hypertension (p<0.001) and to be undergoing in a greater percentage corticosteroids ±immunosuppressors (p<0.001) and low dose ASA (p<0.001) i.e. they presented a greater prevalence of disease features potentially associated with a worse cardiovascular outcome.

Table 1. Demographic, clinical, serological and therapeutic features of the 601 SSc patients subdivided according to the treatment subgroup

FEATURES	**No vasodilators (n=153)**	**Vasodilator therapy (n=448)**	**P**
Female Sex	134/153 (87%)	395/448 (88%)	0.88
Age (mean±SD) years	55±14	57±13	0.21
Age ≥ 50 years	95/153 (62%)	332/448 (74%)	**0.005**
Early disease	53/145 (36%)	148/428 (35%)	0.69
Clinical subset			
Limited cutaneous	124 (81%)	348 (78%)	0.42
Diffuse cutaneous	29 (19%)	100 (22%)	0.42
Serological subset			
Antinuclear antibodies (ANA) positive	134/137 (98%)	400/410 (98%)	0.99
Anti-centromere (ACA) positive	64/137 (47%)	163/410 (42%)	0.16
Anti-Scl-70 positive	39/130 (30%)	136/388 (35%)	0.33
Further aspects			
Baseline Myocardial Disease	18/123 (15%)	56/353 (16%)	0.27
Digital ulcers (ever)	50/149 (33%)	168/437 (38%)	0.33
Tendon friction rubs	7/148 (5%)	20/432 (5%)	0.99
Arthritis	18/153 (12%)	52/442 (12%)	0.99
EScSG activity index≥3	13/153 (8%)	41/448 (9%)	0.87
Systemic arterial	0/153	139/448 (31%)	**<0.001**

Hypertension Cigarette smoking ever Hypercholesterolemia	 39/127 (31%) 0/7	 88/350 (25%) 0/23	 0.24 -
Ongoing corticosteroids ± immunosuppressors	44/145 (30%)	215/408 (53%)	**<0.001**
Ongoing low dose acetylsalicylic acid	28/146 (19%)	205/377 (54%)	**<0.001**

Occurrence of myocardial disease features during follow-up

During 914 follow-up patient/years, ventricular arrhythmias developed in 12 patients; Q waves developed in 5, cardiac blocks in 40, a Pacemaker was implanted in 6; 15 developed a LVEF<55% and/or a CHF. No patient underwent a sudden cardiac death. In univariate analysis, vasodilator therapy resulted to be associated with a nearly significant occurrence of ventricular arrhythmias (7/285 events (2%) occurring during 709 patient/years as compared to 5/97 (5%) during 206 patient/years in those not treated with any vasodilator) (HR 0.33 95%CI 0.10-104; p=0.060); low dose ASA with a reduced incidence of Q waves and/or cardiac blocks and/or pacemaker implantation (17/161 events (10%) occurring during 434 patient/years as compared to 29/182 (16%) during 383 patient/years in those not treated with ASA) (HR 0.41 95%CI 1.98-16.56; p=0.004). On the contrary, male sex (HR 5.73; 95%CI 1.98-16.56; p=0.002) and a EScSG activity index ≥ 3 at the enrollment into the study (HR=4.83; 95%CI 1.52-15.34;p=0.008) were found to predict the development of a LVEF<55% and/or CHF.

In order to perform the multivariate Cox regression analysis, five covariates were selected because of their potential value in influencing the occurrence of cardiac events over time. Several tentatives were performed by selecting, according to the number of the events occurred, all the 5 covariates were considered for cardiac blocks and/or Q waves and/or pacemaker implantation; 2 covariates for ventricular arrhytmias; 2 covariates for LVEF<55% and or CHF. Table 2 shows the results of this approach: vasodilator therapy resulted to be associated with a lower incidence of ventricular arrhythmias (HR 0.28; 95% CI 0.09-0.90; p=0.03); low dose ASA with a lower incidence of cardiac blocks and/or Q waves and/or pacemaker implantation (HR 0.46; 95% CI 0.24-0.87; p=0.02) ; a EScSG activity index≥3 with a higher occurrence of a LVEF<55% and/or CHF (HR 3.71; 95% CI 1.02-13.42;p= 0.05) and cardiac blocks and/or Q waves and/or pacemaker implantation

(HR 2.15; 95% CI 1.00-4.63; p=0.05). Moreover, an unfavourable role of male sex emerged.

Finally, since therapeutic strategies can differ among distinct centres, a Cox frailty survival model with center of enrollment as random effect, was performed (Table 3). The associations of vasodilators, low dose ASA and an EScSG activity index≥3 were confirmed.

Table 2. Associations detected for each outcome measure by multivariate Cox regression analysis

COVARIATES	Cardiac Blocks and/or Q waves and/or Pacemaker Implantation n.events=49* HR; 95%CI; p	Ventricular Arrhytmias n. events=12 HR: 95%CI; p	LVEF≤ 55% and/or CHF n.events=19 HR: 95%CI; p
Male sex		-	**5.70: 2.20-18.9; <0.001**
Age≥50			-
EScSG activity index ≥3	**2.15; 1.00-4.63; 0.05**	-	**3.71; 1.02-13.42; 0.05**
Low dose ASA	**0.46; 0.24-0.87; 0.02**	-	
Vasodilators		**0.28; 0.09-0.90; 0.03**	-

***Two patients developed 2 events (1 Cardiac Block and Pacemaker Implantation; 1 Cardiac Block and/or Q wave)**

Table 3. Associations detected for each outcome measure by Cox frailty analysis

COVARIATES	Cardiac Blocks and/or Q waves and/or Pacemaker Implantation n.events=49* HR; 95%CI; p	Ventricular Arrhytmias n. events=12 HR; 95%CI; p	LVEF≤ 50% and/or CHF n.events=19 HR; 95%CI; p

EScSG activity index ≥3	**2.12; 0.98-4.57; 0.06**	-	**3.79; 1.04-13.82; 0.04**
Low dose ASA	**0.53; 0.26-1.08; 0.08**	-	**-**
Vasodilators	-	**0.32; 0.10-1.02; 0.05**	-

*** Two patients developed 2 events (1 Cardiac Block and Pacemaker Implantation; 1 Cardiac Block and/or Q wave)**

Withdrawal from vasodilator therapy and low dose ASA

Ninety-three out of the 448 patients undergoing vasodilator therapy withdrew from treatment: 15 treated with CCB alone, 3 treated with ACEi or AngIIrb alone, none with CCB + ACEi or AngIIrb reaching an incidence of 2.1/100 patient-years; 31 treated with endothelin receptor antagonists, 19 treated with phosphodiesterase type 5 inhibitors and 25 treated with prostanoids reaching an incidence of 32/100 patient-years. Moreover, 16 of the 230 patients undergoing ASA withdrew from treatment reaching an incidence rate of 3/100 patient-years.

DISCUSSION

To the best of our knowledge, this is the first observational, prospective, long term study to investigate the association between vasodilator therapy and the occurrence of disease manifestations probably or potentially related to myocardial ischemia (ventricular arrhythmias), fibrosis (Q waves and/or cardiac blocks and/or pacemaker implantation) or both (reduced LVEF, congestive heart failure and sudden cardiac death). Actually, as far as the influence of vasodilator therapy on myocardial disease is concerned, Kazzam et al.[27] only investigated diastolic and systolic function in 22 SSc patients receiving captopril treatment (1.3 mg/ kg/ daily) for 11-15 months. These authors found an increase in LVEF and a decrease in isovolumic relaxation time, indicating an improved left ventricular filling, but did not consider any of the features assessed in our study.

In order to address the aim of the study, we also investigated the association between the occurrence of the investigated manifestations and demographic, disease and different therapeutic aspects potentially involved in SSc cardiac disease.[1-3,18-23] After excluding any bias deriving from potential differences in the treatment policies among the distinct centres involved in the study, vasodilators were found to be associated with a lower

incidence of ventricular arrhythmias, low dose ASA with a nearly significant, lower incidence of cardiac blocks and/or Q waves and/or pacemaker implantation; active disease, as defined by a EScSG activity index ≥3 at enrollment with a higher incidence of a reduced LVEF and/or CHF.

We underwent our prospective study because of the commonly shared opinion on the implication of ischemia/reperfusion events in the induction of myocardial fibrosis in SSc,[1-4] as well as the evidence emerged by short term trials and retrospective observational studies suggesting a beneficial effect of vasodilators on cardiac vascularization and function in the disease.[5-11] We could not confirm the retrospectively detected association between vasodilators use and a preserved LVEF,[10] neither we detected any association between vasodilators and a reduced incidence of cardiac blocks and/or Q waves and/or pacemaker implantation, which are distinct manifestations of myocardial fibrosis or of a therapeutic intervention promoted by its consequences.[12] Nevertheless, we pointed out an association between vasodilators and a lower incidence of ventricular arrhythmias, which likely depend on ischemic processes.[13,14] This result deserves to be underlined since ventricular arrhythmias have long been known to be associated with a poor prognosis in SSc.[13-14,21]

Investigating different aspects potentially associated with the incidence of cardiac events, we happened to point out an unexpected protective role of low dose ASA and an unfavourable prognostic role of the EScSG activity index.

Low dose ASA is currently prescribed to patients with a high risk of coronary artery disease.[23] Moreover, it has been recently reported to be associated with a decrease in the occurrence of major cardiovascular events (i.e. myocardial infarction and stroke) in patients with systemic lupus erythematosus[27-28] and rheumatoid arthritis.[29] It might, therefore, be hypothesized that the associations detected between the reduction in the occurrence of distinct cardiac events and low dose ASA do not depend on a potential protective effect on small intramyocardial coronary artery disease. Nevertheless, platelet activation has been reported to play a role of both vascular and fibrotic manifestations of SSc.[30] Moreover, markers of platelet activation have long been known to be responsive to antiplatelet therapy.[31]

As far as EScSG activity index, Nevskaya et al.[19] have recently reported a predictive role of the severity heart disease accrual by its adjusted mean over 3 years. Our results seem to indicate that even a single evaluation might have a prognostic meaning. This result

prospects that achieving a EScSG activity index≥3 might be a target at least in clinical practice.

In the original design of our study, we had envisaged 3 treatment arms i.e. CCB, ACEinh, CCB +ACEinh. Actually, we had not considered the possibility of a SSc patient who is not prescribed any vasodilator drug. This does not appear to be the case, our data on prospectively enrolled patients from 20 EUSTAR centres confirming those reported by the German SSc network highlighting the high percentage of SSc patients who do not receive any vasoactive therapy.[32]

The observational nature of the study does not allow to prospect any cause/effect relationship. Well designed Randomised Controlled Trials (RCTs) are needed to either support or refuse any therapeutic role of vasodilators and low dose ASA in the prevention of myocardial disease in SSc patients. In addition, the variable, non-standardised length of follow-up represents a limitation, that, however, appears to be balanced by the long cumulative duration of follow-up (914 patient/years) and its median time (2.4 years).

Vascular disease has long been considered a pathological hallmark of SSc.[33] The low incidence of withdrawls from vasodilator therapy and low dose ASA in our study, even if waiting for the results of properly designed RCTs, might suggest to consider adding low dose ASA and a vasodilator agent to the therapeutic strategy of any SSc patients. In that regard, given the apparent protective role of CCB for SRC on one side,[34] and the increased risk of death associated with previous exposure to ACEinh in patients developing a SRC,[35] it appears advisable to start with a CCB and to add an ACEinh in patients with diastolic dysfunction for the known effect of the latter on ventricular filling.[26]

In conclusion, our prospective, observational study suggests a protective role of vasodilators and low dose ASA on distinct manifestations of SSc myocardial disease and prospects the opportunity to conduct well designed RCTs on both therapeutic strategies.

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Contributors: Study conception and design: GV, UML, CPD, FDG, GR, LC, MMC, OD, UAW, YA. Acquisition of data: AR, SF, RI, VM, SG, BM, JA, IHT, MF, ES, VL, SN, VKJ, GA, LPA, AMG, CM, JH, TS, AV, SM, IF, AG, BKL,SR. Analysis and interpretation of data: GV, DH, AR, SF. Revising the article: GV, BM, IHT, LC, CPD, UAW, YA, UML.

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Competing interests: none

Ethics approval: All contributing EUSTAR centres have obtained approval from their respective local ethics committee for including patients data in the EUSTAR database and patients have provided an informed consent according to local ethical requirements.

Key messages:

What is already known about this subject?

- Short term studies have underlined a beneficial effect of calcium channel blockers (CCB) and other vasodilators including angiotensin converting enzyme inhibitors (ACEinh) on cardiac vascularization and function in Systemic Sclerosis (SSc).
- However, the role of vasodilative agents in the prevention of primary myocardial disease has not yet been defined.

What does this study add?

-This is the first observational, long term study to investigate the association between vasodilators use and the occurrence of disease manifestations probably or potentially related to myocardial fibrosis.
- Associations between vasodilators and low dose ASA use and a decrease in the incidence of distinct manifestations have emerged.

How might this impact on clinical practice?

-Our study could prompt clinicians to consider adding a vasodilator agent and low dose ASA to the therapeutic strategy of any SSc patient.

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