Brief Report

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May Combination Therapy with Endothelin Receptor Antagonist and PDE5 Inhibitors Prevent Echocardiographic Findings Suspicious for PAH? Description of a Real-Life Case Series

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May Combination Therapy with Endothelin Receptor Antagonist and PDE5 Inhibitors Prevent Echocardiographic Findings Suspicious for PAH? Description of a Real-Life Case Series

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Abstract: Objective: to retrospectively evaluate the incidence rate (IR) of echocardiographic signs suspected for pulmonary hypertension (PH) in Systemic sclerosis (SSc) patients after the introduction of a combination therapy with bosentan and sildenafil for treatment or prevention of digital ulcers. Methods: patients attending the Scleroderma Unit of the Universital Hospital of Careggi from July 2010 to July 2023 were enrolled. Patients older than 18 years old, with an history of digital ulcers, treated with bosentan and sildenafil in combination for at least 12 months were included. Patients with a diagnosis of PH preceding the introduction of the therapy were excluded. Demographical data, disease duration, laboratoristic and instrumental data (pulmonary function tests, echocardiographic estimation of pulmonary artery pressure (PAPs) and ultrasonographic value of renal resistive index) were collected. The IR of echocardiographic signs suspected for pulmonary hypertension and their 95% confidence interval were calculated in events/1000 patients-years.Results: forty-seven patients were enrolled; mean disease duration was 12,14 years (SD 5,87). Mean duration of the combination treatment was 78.33 (SD 41.37) months and total at-risk time was 3525 months. Two patients (4,2%) presented echocardiographic signs of PH (sPAP 50 mmHg and 40 mmHg); the IR was calculated to be 6.8/1000 patients-years (95% CI 6,02-7,7). In one of the 2 patients RHC excluded PAH, while the other patient refused to undergo to RHC and PAH could not be confirmed/excluded. A stability of PFTs and echocardiografic PAPs was observed during the observation time. Conclusions: the results of this retrospective study suggest that combination therapy with endothelin receptor antagonist and Phosphodiesterase-5 (PDE5) inhibitors could help in preventing PAH in SSc; prospective case-control studies on larger population are needed to improve knowledge in this field.

Keywords: systemic sclerosis; pulmonary hypertension; Phosphodiesterase-5 inhibitors; endothelin receptor antagonist

1. Introduction

Systemic Sclerosis (SSc) is a chronic connective tissue disease characterized by vasculopathy, inflammation with activation of the immune system and production of specific antibodies and fibrosis of skin and internal organs [1]. Nowadays, an early recognition of the disease and a propt treatment, along with a constant follow up, permit to reduce SSc morbidity and mortality, but severe manifestations are still a challenge fo rheumatologist involving in SSc management. Moreover, as the expectancy of life for SSc patients grew up, new needs in treating a long-standing disease are emerging. Pulmonary arterial hypertension (PAH) is a serious complication of SSc vasculopathy, representing one of the main causes of SSc-related deaths together with interstitial lung disease (ILD)[2] Pulmonary hypertension (PH) is a hemodynamic state defined by a mean pulmonary arterial pressure (mPAP)>20 mmHg at rest at right heart catheterization (RHC) that still represents the gold

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standard diagnostic test. PH may be caused by different clinical conditions, often requiring a multidisciplinary approach, and it is clinically classified in five groups[3]: PAH (group 1), PH associated with left heart disease (group 2), PH associated with lung disease and/or hypoxia (group 3), PH associated with pulmonary artery obstructions (group 5) and PH with unclear and/or multifactorial mechanisms (group 6).

SSc patients may present different clinical conditions associated with PH, in fact aside from PAH, patients can develop group 2 PH due to left-heart dysfunction, group 3 PH because of ILD, and, less commonly, pulmonary veno-occlusive disease (group 1). In this context, a previous study reported 19% of PAH, 6% of group 2 PH and 6% of group 3 PH among 466 SSc patients subjected to RHC[4]. Differentiate between these groups is mandatory to establish the prognosis and to select the more appropriate treatment.

The prevalence of PAH within the SSc population is estimated between 6.4% and 9%[5], varying particularly according to the disease subset. The incidence of SSc-PAH in patients with limited cutaneous SSc and diffuse cutaneous SSc is estimated to be 1.25 and 0.4 cases per 100 patient-years, respectively[6]. During the last period, both innovation in the treatment and timely diagnosis of PAH improved its prognosis but mortality rate remains high with three years survival rate of 62%[7] and an estimated 10-year survival rate of only 26.8%[8]. The prognosis of SSc patients with PAH is strongly linked to the early detection of PAH and for this reason, the prompt identification of patients at major risk to develop this complication is mandatory. Major risk factors for PAH development include the positivity of anti-centromere antibodies (ACA), extensive telangiectasias and longer disease duration[9].

In addition, PAH in SSc seems to have a worst outcome than the idiopathic form and now no prevention pharmacological strategy has been individuated to prevent this life-threatening condition[10]. Moreover, the response to specific PAH therapies is linked to the function class at time of diagnosis and for all these reasons, over the years different screening processes have been proposed to early detect this condition[11]. Among these, the DETECT (detection of pulmonary arterial hypertension in SSc), the ASIG (Australian Scleroderma Interest Group) and the ITINER-Air (French multicenter transversal observational study) are composite algorithms commonly available in clinical practice[12]

Beyond these screening algorithms, echocardiographic parameters are widely used as screening tools for PAH, in particular systolic pulmonary arterial pressure (sPAP) that is also included in the French model. Others echocardiography parameters are evaluated in clinical practice, as the tricuspid regurgitation velocity (TRV) and the right atrium area, both included in the DETECT algorithm. In addition to echocardiography, other examinations are routinely performed in SSc patients as screening tools for PAH, including pulmonary function test (PFTs) with particular attention to lung diffusion for carbon oxide (DLCO) and biomarkers as the N-terminal pro-B-type natriuretic peptide (NT-proBNP). Among clinical manifestations, the presence of unexplained dyspnoea is a unspecific symptom that may indicate the presence of PAH and must lead to an instrumental evaluation.

In this context, the recent ESC/ERS guidelines for the diagnosis and treatment of PH remarked the importance of echocardiography as the first-line, non-invasive, diagnostic investigation in suspected PH particularly assessing the TRV and the presence of other signs suggestive of PH.

Once SSc-related PAH is diagnosed, therapies are based on underlining pathogenetic pathway and patients' risk assessment including prostacyclin analogs, endothelin receptor antagonists (ERA), phosphodiesterase isoenzyme 5 inhibitors (PDE5is) and guanylate cyclase stimulator (riociguat). According to the ESC guidelines, patients in the high-risk group should start PAH pharmacotherapy with a combination of triple therapy containing ERA, PDE5i and parenteral prostacyclin. Patients with low- or intermediate-risk should start with dual combination therapy containing ERA and PDE5i or riociguat.

Among the vascular therapeutic options for SSc, ERAs account for both vasodilating and anti-fibrotic properties and bosentan, a dual ERA, has proven effective to heal active ulcers[13] and to prevent their recurrence. PDE5s, as sildenafil, promote vascular smooth muscle relaxation and

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vasodilatation[14]. For this reason, both bosentan and sildenafil are widely use in patients with PAH and they are also indicated in treating digital ulcers (DUs) and Raynaud's phenomenon, respectively.

The aim of this retrospective study is to evaluate the incidence of echocardiographic signs suspected for PH, in particular sPAP, in SSc patients treated with with bosentan and sildenafil for peripheral vasculopathy (active DUs or prevention of their recurrence).

2. Materials and Methods

SSc patients attending the Scleroderma Unit of Universital Hospital of Careggi from July 2010 to July 2023 were enrolled in a retrospective observational study. Inclusion criteria were: age≥18 years old, to be classified as SSc according to ACR/EULAR 2013 classification criteria[15], an history of digital ulcers (DUs), to be treated with bosentan and sildenafil in combination since at least 12 months and to have echocardiographic evaluation at baseline (time of bosentan and sildenafil introduction) and at the end of the observation period . Bosentan was administered at a dosage of 125 BID die; sildenafil was administered at a dosage of 20 mg TID die. Patients with a diagnosis of PAH or PH at RHC preceding the introduction of the therapy were excluded from the study.For each patient, demographical data, disease features (SSc-specific antibodies, renal arterial resistive index assessed by ultrasound examination), data on combination therapies were collected at baseline. In addition, echocardiographic parameters (sPAP) and PFTs values (forced vital capacity (FVC) and DLCO expressed as percentage of theorical measures) were collected for all patients at baseline and at the end of the observation period. We considered sPAP> 40mmHg the echocardiographic sign to suspect the presence of PH.

Statistical analysis was made through software R 3.5.2 GUI 1.70 El Capitan build (7612). Categorical variables were described using frequencies and percentages, numerical variables were described by mean and standard deviation. The incidence rate of echocardiographic signs suspected of pulmonary hypertension (sPAP> 40mmHg) in the study population and its 95% confidence interval were calculated in events/1000 patients-years. When available, data of RHC were recorded, defining a case of PAH a mean pulmonary arterial pressure (mPAP) 25 mmHg, a pulmonary capillary wedge pressure (PCPw) of 15mmHg and pulmonary vascular resistance>3 Wood units[16].

Baseline and follow up PFTs and PAPs were compared using paired T test, with significancy levels fixed at 5%.

The study was approved by the Ethical Committee of Florence: 37/2008. All patients gave their written informed consent.

3. Results

47 patients, with a diagnosis of SSc and past or active DUs received a vasoactive treatment with bosentan and sildenafil for at least 12 months and were enrolled in the study. Among them, 42 (89,4%) were female; the mean age was of 57,87 years old (SD 14,87) and the mean disease duration was 12,14 years (SD 5,87). 21 patients (44,7%) were positive for anti-topoisomerase I (anti-topo I) antibodies, while 16 (34%) were ACA positive. Five patients did not have SSc-specific antibodies neither other autoantibody 'positivity. Eleven (23.4%) patients had a lungs'involvement with the presence of interstitial lung disease.

Regarding concomitant vasodilator therapies, 11/47 patients (23,4%) were also treated with periodical Iloprost infusions.

The mean duration of the treatment was 78.33 (SD 41.37) months and total at-risk time was 3525 months.

In Table 1, populations characteristics and baseline laboratoristic and instrumental data (NT-proBNP, PFTs parameters, echocardiographic sPAP and RI values) are reported. As described, the mean basal sPAP was within the range of normality.

Among all patients, only 2 patients (4,2%), at the end of follow up, presented echocardiographic signs of pulmonary hypertension (sPAP≥40 mmHg) with a sPAP of 50 mmHg and 40 mmHg, respectively. The incidence rate of echocardiographic sign of PH was calculated to be 6.8/1000 patients-years (95% CI 6,02-7,7)

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Table 1.

Sex, n°(%)	
Females	42 (89.4)
Males	5 (10.6)
Age, mean (SD)	12.14 (5.87)
Disease duration, mean (SD)	57.87 (14.87)
Autoantibodies, n° (%)	
ACA	16 (38.1)
anti-topo I	21 (50.0)
Anti-RNP	1 (2.4)
Anti Pm/Scl	1 (2.4)
Anti Ro52	2 (4.8)
Anti Sm	1 (2.4)
Presence of ILD, n° (%)	11 (23.4)
FVC (%), mean (SD)	98,61 (16,66)
DLCO (%), mean (SD)	69,61 (18,84)
PAPs (mmHg), media (SD)	28,16 (5,60)
NT-proBNP (pg/mL), mean (SD)	327,71 (528,85)
Renal resistive index	70,72 (4,71)

Baseline clinical, laboratoristic and instrumental data.

RHC was proposed to both patients with echocardiographic signs of pulmonary hyper tension but one refused this examination. In the other patient, RHC showed hemodynamic findings compatible with mild post-capillary PH and PAH was ruled out. As reported in Table 2, a stability in PFTs values and echocardiographic sPAP, was observed from baseline to the end of follow up in the studied population. No scleroderma renal crisis was recorded during the observation period.

Table 2.

	BL	FU	p value
FVC (%), mean (SD)	98,61 (16,66)	99,59 (25,10)	0.777
DLCO (%), mean (SD)	69,61 (18,84)	69,61 (18,84)	0.938
PAPs (mmHg), media (SD)	28,16 (5,60)	29,21 (7,16)	0.171

Comparison between functional and echocardiographic baseline and follow up values.

4. Discussion

PAH is due to a proliferative remodeling of small pulmonary arteries representing a fearful manifestation of SSc and according with the 2022 ESC/ERS guidelines it is hemodynamically defined as a pre-capillary PH (in the absence of other causes of pre-capillary PH) with a mPAP >20 mmHg, a PAWP (pulmonary arterial wedge pressure) ⩽15 mmHg and a PVR (pulmonary vascular resistance)>2 WU at RHC. The prevalence of PAH within the SSc population is highly variable, particularly according to the disease subset. Major risk factors for PAH development include the positivity of anti-centromere antibodies, longer disease duration and the presence of other signs of vasculopathy, as extensive cutaneous telangiectasia[17], digital ulcers[18] and digital pitting scars[19]. PAH remains a major cause of death in SSc patients, however over the last years the management of this complication has certainly improved thanks to the use of new drugs. In this context, the AMBITION trial[20] showed the goodness of early introduction of combination therapy with once-daily ambrisentan and tadalafil, as compared with monotherapy with either of these agents, having as primary outcome a composite end point of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. However, to our knowledge few studies evaluated the incidence of new PAH cases in SSc patients treated with vasoactive drugs

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because of the presence of DUs. Castellvì et al[21] conducted a retrospective case-control study in 237 SSc patients with previous history of DUs and compared the occurrence of new PH echocardiographic diagnosis in patients treated (n=59) and not-treated (n=163) with bosentan for at least one month. The median treatment duration was of 34 (95% CI 5–59) months. During the follow-up, 13.8% of treated patients with bosentan and 23.7% of no treated developed PH based on echocardiography definition (OR = 0.52; CI95% = 0.22–1.19) without significant differences between the two groups. However, authors performed a multivariate analysis finding that patients without bosentan had a baseline higher risk to develop PH (3.91 (IC95%:1.3–11.6; p<0.02) so that bosentan could have been protective against PH in this group. Caramaschi et al[22] evaluated the incidence of PH in 81 patients treated with cyclic iloprost infusion for severe Raynaud phenomenon and/or DUs. At the end of follow up (61.3 +/- 29.3) months, 9 patients presented with echocardiographic signs of PH. One of them, underwent RHC which excluded PAH. Even if the incidence rate of PH in this study was in line with the one reported in literature in larger cohorts, authors stated that none of the included patients developed severe isolated pulmonary hypertension. In 2021, Pestaña-Fernández et al[23] analyzed 544 patients with SSc and an history of DUs. Out of them, 221 was treated with ERA and/or PDE5is, while the other 323 did not receive vasoactive therapy. The incidence rate of PAH diagnosed on the basis of RHC resulted 7.7 (95% CI 4.7, 12.0) per 1000 person-years in the treated group compared with 7.8 (95% CI 5.2, 11.3) per 1000-person years (p value of 0.988) in the no-treatment group. The incidence rate difference between groups did not achieve statistical significance [0.1 (4.8, 4.69); p 0.988]. The authors stated that patients treated with ERA and or PDE5is could show a more severe vascular involvement. Moreover, a longer time between the DUs' presentation and scleroderma renal crisis development was observed so that vasoactive drug could exert a protective role. However, authors did not perform a sub analysis to compare patients in monotherapy and patients in combination therapy with ERA and PDE5is.

Our study evaluated the presence of echocardiographic signs of PH in patients treated with combination therapy with bosentan and sildenafil for peripheral vasculopathy, reveling that only 2/47 patients showed an increase in sPAP at the end of the observation period (56 and 130 months). One patients was subjected to RHC and a mild post-capillary PH was diagnosed. Unfortunately, one of two patients with increased sPAP at follow-up refused the RHC which may not have confirmed the presence of a PAH, reinforcing the hypothesis that the combo-therapy could be preventive for PAH development. Overall, our data reported a stabilization of echocardiography parameters in patients treated with bosentan and sildenafil suggesting a potential preventive role of this combination therapy in the development of instrumental alterations suggestive of PH. As above reported, echocardiography represents the first-line, non-invasive, diagnostic investigation in suspected PH. Therefore, from a clinical point of view, the data of our study translate into a low number of patients candidate for RHC which represents a more (even if minimally) invasive examination.

Our study presents some limitation: first of all, the lack of a control group, however justified by our clinical practice . In fact, in our center all patients with DUs or with history of DUs are candidates for combination therapy with a vasoactive treatment (bosentan) and with a vasodilator (sildenafil or iloprost) if no contraindications are present. Therefore, the control population (patients not treated with bosentan and sildenafil) at our disposal was represented by SSc subjects without DUs that are known themselves to represent a severe sign of peripheral vascular disease associated with PAH. In addition, the only echocardiographic parameter available for all patients at baseline and follow-up were represented by sPAP, while data on TRV and right atrium area were available for few patient not allowing a statistical analysis of these values. Other limitations of our study include the small sample size, its retrospective nature, and the relatively short follow up that prevent from doing definitive comparison with PAH epidemiological data. Anyway, in our population, the low incidence of increased values of sPAP, along with the stability of PFT parameters allow to be optimist toward the protective role of the combination therapy against SSc PAH indicating that its routinary administration in patients with severe Raynaud phenomenon/DUs could help in lowering the incidence and the mortality rate of this challenging SSc complication.

In conclusion, the results of this retrospective study suggest the possible role of combination therapy with bosentan and sildenafil in preventing PH in SSc. The confirmation of a preventive role of a combination therapy of endothelin antagonist receptors and phosphodiesterase-5 inhibitors against PAH development in SSc patients now need further prospective studies in a larger cohort of patients considering potential confounders as the presence of peripheral vasculopathy (DUs or teleangectasias).

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Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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References

1. Varga, J.; Trojanowska, M.; Kuwana, M. Pathogenesis of systemic sclerosis: Recent insights of molecular and cellular mechanisms and therapeutic opportunities. J. Scleroderma Relat. Disord. 2017, 2, 137–152.https://doi.org/10.5301/jsrd.5000249
2. Steen, V.D.; Medsger, T.A. Changes in causes of death in systemic sclerosis, 1972–2002. Ann. Rheum. Dis. 2007, 66, 940–944. https://doi.org/10.1136/ard.2006.066068
3. Humbert M., Kovacs G., Hoeper M.M.,et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG) Eur. Heart J. 2022;43:3618–3731. doi: 10.1093/eurheartj/ehac237
4. Steen, V.D.; Medsger, T.A. Changes in causes of death in systemic sclerosis, 1972–2002. Ann. Rheum. Dis. 2007, 66, 940–944. https://doi.org/10.1136/ard.2006.066068.
5. Rubio-Rivas M, Homs NA, Cuartero D, Corbella X. The prevalence and incidence rate of pulmonary arterial hypertension in systemic sclerosis: Systematic review and meta-analysis. Autoimmun Rev. 2021 Jan;20(1):102713. doi: 10.1016/j.autrev.2020.102713. Epub 2020 Nov 13. PMID: 33197579.
6. Haque A, Kiely DG, Kovacs G, Thompson AAR, Condliffe R. Pulmonary hypertension phenotypes in patients with systemic sclerosis. Eur Respir Rev. 2021 Aug 17;30(161):210053. doi: 10.1183/16000617.0053-2021. PMID: 34407977; PMCID: PMC9517999.
7. Morrisroe K, Stevens W, Huq M, et al; Australian Scleroderma Interest Group (ASIG). Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension. Arthritis Res Ther. 2017 Jun 2;19(1):122. doi: 10.1186/s13075-017-1341-x. PMID: 28576149; PMCID: PMC5457656.
8. Chen X, Quan R, Qian Y, et al, 10-year survival of pulmonary arterial hypertension associated with connective tissue disease: insights from a multicenter PAH registry. Rheumatology (Oxford). 2023 Mar 13:kead103. doi: 10.1093/rheumatology/kead103. Epub ahead of print. PMID: 36912696.
9. Shah AA, Wigley FM, Hummers LK. Telangiectases in scleroderma: a potential clinical marker of pulmonary arterial hypertension. J Rheumatol. 2010 Jan;37(1):98-104. doi: 10.3899/jrheum.090697. Epub 2009 Dec 1. PMID: 19955048; PMCID: PMC3419384.

10. Launay D, et al. Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. Ann Rheum Dis 2013;72(12):1940–6
11. Screening for pulmonary arterial hypertension in systemic sclerosis: A systematic literature review.Bruni C, De Luca G, Lazzaroni MG, Zanatta E, Lepri G, Airò P, Dagna L, Doria A, Matucci-Cerinic M.Eur J Intern Med. 2020 Aug;78:17-25. doi: 10.1016/j.ejim.2020.05.042. Epub 2020 Jun 12.PMID: 32540411 Review
12. Bruni C, De Luca G, Lazzaroni MG, Zanatta E, Lepri G, Airò P, Dagna L, Doria A, Matucci-Cerinic M. Screening for pulmonary arterial hypertension in systemic sclerosis: A systematic literature review. Eur J Intern Med. 2020 Aug;78:17-25. doi: 10.1016/j.ejim.2020.05.042. Epub 2020 Jun 12. PMID: 32540411.
13. Hughes M, Bruni C, Ruaro B, Confalonieri M, Matucci-Cerinic M, Bellando-Randone S. Digital Ulcers in Systemic Sclerosis. Presse Med. 2021 Apr;50(1):104064. doi: 10.1016/j.lpm.2021.104064. Epub 2021 Feb 3. PMID: 33548375.
14. Heresi GA, Minai OA. Bosentan in systemic sclerosis. Drugs Today (Barc). 2008 Jun;44(6):415-28. doi: 10.1358/dot.2008.44.6.1220138. PMID: 18596996.
15. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Annals of the rheumatic diseases*. 2013;72(11):1747–55. 10.1136/annrheumdis-2013-204424
16. Galiè N, Humbert M, Vachiery JL, et al, 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119. doi: 10.1093/eurheartj/ehv317. Epub 2015 Aug 29. PMID: 26320113.
17. Hurabielle C, Avouac J, Lepri G, de Risi T, Kahan A, Allanore Y. Skin Telangiectasia and the Identification of a Subset of Systemic Sclerosis Patients With Severe Vascular Disease. Arthritis Care Res (Hoboken). 2016 Jul;68(7):1021-7. doi: 10.1002/acr.22766. PMID: 26474084.
18. Mihai C, Landewé R, van der Heijde D, Walker UA, Constantin PI, Gherghe AM, Ionescu R, Rednic S, Allanore Y, Avouac J, Czirják L, Hachulla E, Riemekasten G, Cozzi F, Airò P, Cutolo M, Mueller-Ladner U, Matucci-Cerinic M; EUSTAR co-authors. Digital ulcers predict a worse disease course in patients with systemic sclerosis. Ann Rheum Dis. 2016 Apr;75(4):681-6. doi: 10.1136/annrheumdis-2014-205897. Epub 2015 Feb 16. PMID: 25688073
19. Hughes M, Heal C, Henes J, Balbir-Gurman A, Distler JHW, Airò P, Müller-Ladner U, Hunzelmann N, Kerzberg E, Rudnicka L, Truchetet ME, Stebbings S, Tanaka Y, Hoffman-Vold AM, Gabrielli A, Distler O, Matucci-Cerinic M; EUSTAR Collaborators. Digital pitting scars are associated with a severe disease course and death in systemic sclerosis: a study from the EUSTAR cohort. Rheumatology (Oxford). 2022 Mar 2;61(3):1141-1147. doi: 10.1093/rheumatology/keab510. PMID: 34146098.
20. Galiè N, Barberà JA, Frost AE, et al, AMBITION Investigators. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. N Engl J Med. 2015 Aug 27;373(9):834-44. doi: 10.1056/NEJMoa1413687. PMID: 26308684
21. Castellví I, Simeón CP, Sarmiento M, Casademont J, Corominas H, Fonollosa V. Effect of bosentan in pulmonary hypertension development in systemic sclerosis patients with digital ulcers. PLoS One. 2020 Dec 10;15(12):e0243651. doi: 10.1371/journal.pone.0243651. PMID: 33301540; PMCID: PMC7728198.
22. Caramaschi P, Volpe A, Tinazzi I, Bambara LM, Carletto A, Biasi D. Does cyclically iloprost infusion prevent severe isolated pulmonary hypertension in systemic sclerosis? Preliminary results. Rheumatol Int. 2006 Dec;27(2):203-5. doi: 10.1007/s00296-006-0222-4. Epub 2006 Sep 28. PMID: 17006704
23. Pestaña-Fernández M, Rubio-Rivas M, Tolosa-Vilella C, et al. The incidence rate of pulmonary arterial hypertension and scleroderma renal crisis in systemic sclerosis patients with digital ulcers on endothelin antagonist receptors (ERAs) and phosphodiesterase-5 inhibitors (PDE5i). Rheumatology (Oxford). 2021;60(2):872-880. doi:10.1093/rheumatology/keaa401