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Review

Preclinical and Clinical Data on Current Therapeutic Options for Micro- and Macrovascular Abnormalities in Systemic Sclerosis

Konstantina Bakopoulou [1], Issa El Kaouri [1], Elina Siliogka [2], Periklis Siliogkas [3], Russka Shumnalieva [4,5] and Tsvetelina Velikova [4,*]

[1] Faculty of Medicine, Medical University Sofia, Boulevard 'Akademik Ivan Evstratiev Geshov' 15, 1431 Sofia, Bulgaria; 104170@students.mu-sofia.bg (K.B.); 104166@students.mu-sofia.bg (I.E.K.)
[2] Faculty of Medicine, National and Kapodistrian University of Athens, Mikras Asias 75, 11527 Athens, Greece; elinasiliogka@gmail.com
[3] General Hospital of Athens Korgialeneio—Benakeio Hellenic Red Cross, Athanasaki 11, 11526 Athens, Greece; periaek1@gmail.com
[4] Medical Faculty, Sofia University St. Kliment Ohridski, 1407 Sofia, Bulgaria; rshumnalieva@yahoo.com
[5] Department of Rheumatology, Clinic of Rheumatology, University Hospital St. Ivan Rilski, Faculty of Medicine, Medical University Sofia, 1612 Sofia, Bulgaria
* Correspondence: tsvelikova@medfac.mu-sofia.bg

Abstract: Background: Systemic sclerosis (SSc) represents a multidimensional disease affecting various organs and systems, with the common denominator being the vascular pathology encountered in the micro- and macrocirculation of SSc patients. Recently, much progress has been made toward understanding the molecular basis of endothelial injury and subsequent fibroblast activation, thus paving the way for specific therapy that can target and counteract these processes. **Aim:** In this review, we examined the latest preclinical and clinical data on therapeutic options to address vascular abnormalities in SSc. **Results:** We discuss the efficacy of current treatments, including pharmacological agents and emerging therapies, in mitigating vascular damage and improving patient outcomes based on preclinical models and clinical trials that offer evidence of their safety and effectiveness. **Conclusions:** Although promising therapeutic strategies emerge, optimizing the management of vascular abnormalities in SSc requires further research.

Keywords: systemic sclerosis; SSc; microvascular abnormalities; macrovascular abnormalities; vascular therapy; autoimmune disease; pharmacological agents; biologics; clinical trials; preclinical models; therapeutic options

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1. Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease of the connective tissue with an unknown and complex pathogenesis [1]. It is primarily characterized by widespread damage, immune dysregulation, and extensive fibrosis of the skin and internal organs [2]. Based on the extent of skin involvement, it is classified into two main subtypes: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (scSSc). lcSSc, typically, involves the skin of the face, neck, and distal extremities, whereas dcSSc affects more extensive skin areas, including the trunk and proximal limbs, and is associated with severe internal organ involvement [2].

The epidemiology of SSc varies geographically, with an estimated incidence of 1–2 cases per 100,000 persons per year and a prevalence of 10–30 cases per 100,000 persons [3]. The disease predominantly affects women, with a female-to-male ratio of approximately 5:1. SSc usually manifests between the ages of 30 and 50, though it can occur at any age [4].

According to the 2013 ACR/EULAR classification criteria [2], the diagnosis of SSc requires a combination of clinical features, including skin thickening, specific autoantibodies, and characteristic capillary changes visible via nail fold capillaroscopy. A study by

Araujo et al. (2017) found that 53% of patients with early SSc exhibited Raynaud's phenomenon (RP), abnormal capillaroscopy, and autoantibodies specific to SSc, underscoring the importance of these criteria in early disease detection [3]. Vascular abnormalities are fundamental in the pathogenesis and progression of SSc. Early in the disease, endothelial cell injury leads to chronic inflammation and subsequent fibrosis, contributing to both skin thickening and internal organ involvement. Microvascular damage is a crucial driver of clinical manifestations such as RP, digital ulcers (DUs), and pulmonary arterial hypertension (PAH) [5]. An increasing number of studies link epigenetic abnormalities—including particular changes affecting the immune cells, endothelial cells, and fibroblasts—to the pathophysiology of SSc, i.e., the function of non-coding RNAs, histone modifications, and DNA methylation, as well as how these epigenetic changes impact clinical manifestations of the disease [6].

The clinical significance of these abnormalities extends beyond localized tissue damage, contributing to systemic complications such as PAH, renal crisis, and increased cardiovascular risk, which significantly impact patient outcomes and quality of life. They are crucial in determining disease severity, progression, and overall prognosis. Therefore, effective monitoring and treating vascular involvement are essential for improving clinical outcomes and quality of life in those affected by SSc [5].

This review aims to summarize the new insights into the pathogenetic treatment of SSc by explaining the mechanisms, clinical features, and diagnostic approach applied in various SSc-specific vascular complications, including RP, DUs, PAH, and the involvement of mesenteric and peripheral arteries.

2. Pathogenesis of Vascular Abnormalities in SSc

2.1. Role of Autoantibodies in Immunopathogenesis of SSc

It has long been postulated that autoantibodies constitute a triggering event in the pathogenesis of SSc. Raschi et al. [7] successfully illustrated that some SSc-specific autoantibodies (anti-Scl70, anti-centromere, and anti-Th/To), when embedded in immune complexes, were essential in causing endothelial damage and vasculopathy.

Many autoantibodies have been associated with different phenotypes of vascular manifestations and/or the risk of vascular involvement. For instance, anti-RNA polymerase III antibodies confer a higher risk of gastroesophageal vascular ectasia, PAH, and renal crisis. Accordingly, anti-centromere, anti-Th/To, and anti-ribonucleoprotein (RNP) antibodies increase the risk of PAH. Digital infarcts and PAH have been associated with the presence of anti-endothelial cell antibodies [8].

2.2. Immune Cell Involvement in SSc

One of the mechanisms implicated in the pathogenesis of SSc is impaired T-cell homeostasis, which is associated with a decrease in the population of regulatory T cells (Tregs), as evidenced by blood and skin lesion analysis in SSc patients [9]. This is partially attributed to Treg conversion into the profibrotic Th2 and Th17 cell populations. Increasing evidence suggests that T-cell proliferation and cytokine secretion play a significant role in initiating SSc, indicating that T lymphocyte colonies, mainly Th2 and Th17, contribute to disease pathogenesis and fibrosis. Th2 cells produce IL-4, IL-5, IL-10, and IL-13—these are described as anti-inflammatory and profibrotic due to their pathognomonic actions as initiators of extracellular matrix (ECM) production and inhibition of Th1 cell function as noted by Bellando et al. [10].

Different phases of immune polarization have also been proposed, with Th2 polarization correlating with disease exacerbation, whereas a Th2-to-Th1 shift was shown to predict disease duration. Th2 response involves the secretion of IL-4 and IL-13, while antifibrotic IFN-γ mediates Th1 action. Indeed, polymorphisms in the IFN-γ gene have been found to confer an increased risk of SSc, especially associated with skin involvement [9]. IL-4 induces Th2 cell lineage and is further propagated by a positive feedback loop. Kurizinski et al. [11] propose the theory of skin fibrosis and damage due to the imbalance of Th1/Th2.

In addition, Ko et al. [12] highlight that disease progression is closely linked to Th2 immune polarization, while disease duration is often associated with shifts from Th2 to Th1 cells.

Th17 cells—characterized by their production of IL-17A, IL-17F, IL-21 and IL-22—are elevated in SSc patients with skin manifestations, in contrast to controls of healthy patients [13]. Th17 cells are elevated in the peripheral blood of SSc patients, accumulating at disease sites and participating in several physiological manifestations, including remodeling of the ECM, collagen deposition, and neutrophil recruitment. Bălănescu et al. [14] emphasized the critical role of Th17 in autoimmune tissue injury induction, leading to the characteristic finding of skin manifestations in SSc. Therapeutic targets covering Th17 may be utilized for SSc intervention, providing further insights into SSc pathogenesis [15]. The profibrotic Th2 response is further reinforced by the release of IL-6 by various cells and appears to be the putative cause of endothelial cell (EC) activation and apoptosis [8]. IL-6 is another important mediator of fibrotic processes leading to upregulated collagen transcription, although the exact mechanism has yet to be elucidated. This was further supported by an in vitro analysis conducted on dermal fibroblasts by O'Reilly et al. [16]. Their data demonstrated that the effect of IL-6 is highly dependent on the action of STAT3 and indirectly mediated by the TGF-β signaling pathway and SMAD3. Indeed, following the deletion of the IL-6 gene in animal models with lung fibrosis, the fibrotic processes were diminished. Consistent with this, in a culture of dermal fibroblasts from SSc patients, phospho-STAT3 was found to be increased. Finally, it was also demonstrated that Gremlin (a bone morphogenetic protein antagonist) is induced by IL-6 and mediated by canonical TGf-β signaling. Thus, Gremlin was concluded to be profibrotic, likely promoting vascular remodeling and pulmonary hypertension [16].

Cultures from dermal fibroblasts in SSc patients have demonstrated elevated IL-6 levels, correlated with earlier disease, increased mortality risk, unfavorable skin involvement, and accelerated decline in pulmonary function. Furthermore, these fibroblasts, when compared to normal fibroblasts, were noted to express higher levels of collagen alpha 1 (Col1), alpha-smooth muscle actin (αSMA), and connective tissue growth factor (CTGF). The complex nature of trans-signaling mechanisms involving IL-6 and TGF-β pathways results in cardiac, skin, and lung fibrosis, highlighting the significance of tocilizumab therapy and its effectiveness in limiting fibrosis [17,18].

Another recently described mediator of fibrosis is interleukin-11 (IL-11), a profibrotic cytokine exerting its action under the influence of TGF-β1. Its levels were noted to be increased in early dcSSc and patients with interstitial lung disease (ILD). It has been implicated in fibrotic processes not only in the skin but also in the heart and lungs. Additionally, Steadman et al. discovered that IL-11 influences the release of IL-33 (alarmin) at the early stage in fibroblasts, potentially promoting an inflammatory response, whereas at a later time, the influence ceases and fibrotic processes predominate [19]. Ye et al. suggested that the profibrotic effect of IL-11 might be controlled by blocking the IL-11 trans-signaling pathway through JAK2/STAT3 and sgp130Fc interference [20].

2.3. Mechanisms of Endothelial Dysfunction and Injury in SSc

The initiating stimulus of vascular injury in SSc can be secondary to various precipitants, including idiopathic, environmental, and infectious factors, autoantibody-mediated mechanisms, or oxidative stress caused by reactive oxygen species (ROS) [21]. Repeated cycles of endothelial injury propagate a vicious cycle of apoptosis and cell detachment, impairing vessel integrity. Acting synergistically with this, an imbalance between vasoconstricting (e.g., ET-1) and vasodilating mediators (e.g., NO and prostacyclin) is observed, leading to continuous and prolonged alterations in the vessel tone [9]. After von Willebrand Factor (vWF) release, platelet activation and aggregation result in hypercoagulability, thromboxane secretion (a potent vasoconstrictor), and fibrin deposition [22].

These processes culminate in terminal vessel damage, malfunctioning endothelial junctions with increased permeability of the microvasculature and vessel leak, evidenced by the formation of microvascular hemorrhages and localized edema [22]. The increased

permeability and leaky cell junctions permit the recruitment of macrophages, Th2, Th17, and mast cells, resulting in a perivascular infiltration of pro-inflammatory cells [9].

It was recently reported that senescence of endothelial cells contributed to fibrosis through endothelial-to-mesenchymal transition [23]. Furthermore, cellular senescence is involved in overall SSc pathogenesis via direct alteration of cellular functions or indirect promotion of defective immune surveillance [24]. Chiu et al. confirmed these observations in their studies of skin biopsies of fibrotic lesions of SSc patients [25].

2.4. Biomarkers of Endothelial Damage

Muruganandam et al. concluded that the SSc-associated damage in ECs is evidenced by upregulated expression of E-selectin, vascular cell adhesion protein 1 (VCAM-1) and Intercellular Adhesion Molecule 1 (ICAM-1), vWF, tissue factor, and tissue thrombin. On the other hand, lower levels of thrombomodulin, fibrinolysis, and platelet count were observed in association with vasculopathy and DUs [22]. Angiopoietins (Ang-1 and Ang-2) are responsible for the modulation of EC activation and vessel modeling and growth through their interaction with the Tie2 tyrosine kinase receptor. Imbalance in Ang-1 and Ang-2 levels may have a causative role in vascular destruction and abnormal angiogenesis [26].

The same author suggested that increased levels of metalloproteinase tissue inhibitors, such as TIMP-4, correlated with cardiopulmonary vascular involvement. Additionally, neuropilins (NRP1-2) found on ECs were also flagged as potential predictors of PAH, Dus, and abnormalities in nail fold capillaries. Similarly, circulating levels of IL-18 binding protein were associated with PAH, whereas IL-33 and ST2 had predictive value in DUs and PAH. The levels of slit glycoproteins (Slit1-3) and sirtuin (SIRT1-7) molecules with regulatory function in angiogenesis were also elevated in SSc patients with microvascular involvement [22].

2.5. Fibrotic Processes and Remodeling Affecting Blood Vessels

The nature of the lesions observed in SSc vasculopathy can be destructive (capillary loss) or proliferative (thickening of the vessel wall). Underlying this, a vicious cycle is established with ECM deposition worsening hypoxia and, in turn, reduced oxygen tension, which activates the fibrotic processes [27]. Chronic inflammation prompts fibroblasts to commit to a myofibroblast transition under the influence of ET-1, leading to the intima's hypertrophy, the lumen's narrowing, and eventually vessel obliteration. These changes favor chronic ischemia and endothelial cell and capillary loss [21,27].

Additionally, the endothelial cells undergoing the endothelial-to-mesenchymal transition (EndoMT) following downregulation of their markers, such as CD31 and VE-cadherin, transform into a myofibroblast phenotype associated with increased expression of α-SMA, further reinforcing the fibrotic processes [21].

Dysfunction and/or a decreased number of endothelial progenitor cells (EPCs) hinder new angiogenesis, which, combined with the dysregulated function of the VEGF/VEGFR pathway, contributes to vasculopathy. More specifically, elevated levels of VEGF have been noted in SSc patients, which is associated with a robust angiogenic response and results in chaotic vessel patterns. Conversely, there is also increased expression of VEGF-165, an isoform with anti-angiogenic properties [21]. Pericytes seem to have a double role by directly inhibiting the angiogenic processes and simultaneously enhancing ECM deposition.

Another source of myofibroblast cell transformation occurs under the influence of the proliferator-activated receptor γ (PPAR-γ) pathway. Downregulation of this response promotes adipocyte differentiation into myofibroblasts [8]. Conversely, upregulation of the PPAR-γ pathway inhibits the TGF-β-mediated transdifferentiation of fibroblasts into myofibroblasts, therefore possessing both anti-inflammatory and antifibrogenic properties, preventing collagen and ECM deposition [22].

Subendothelial collagen exposure following injury results in platelet activation, which responds with the release of profibrotic cytokines such as TGF-β and serotonin. Serotonin, through interactions with TGF-β, has been demonstrated to promote ECM deposition.

Platelet-derived microparticles (PMPs) have also been implicated in the fibrotic processes encountered in SSc [8].

2.6. Molecular Mediators of Fibrosis

Many cytokines have been associated with a profibrotic/fibrogenic effect. However, in SSc, the main culprits appear to be TGF-β, IL-4, and IL-13, released mainly by Th2 cells [28]. As already discussed, platelet-derived mediators also have a putative role in fibrotic processes, including platelet-derived growth factor (PDGF), PMPs, and serotonin.

PDGF, specifically, signals through Ras to MAP kinase pathways and influences the activity of NADPH oxidases, resulting in the transcription of factors that increase ECM synthesis [28]. SSc is characterized by an enhanced endogenous potential and expression of thrombin, which, in turn, activates ECs and fibroblasts, inducing collagen synthesis, interfering with the action of matrix metalloproteinases and culminating in enhanced ECM production [22].

2.7. Genetic Markers Associated with Vascular Abnormalities in SSc

Great effort has been put into identifying potential susceptibility genes for SSc-associated vascular involvement. GWAS studies have located an SNP that is found upstream of the gene for the PPAR-γ pathway as a possible target [29,30]. Other less studied genes with, as of yet, unclear functions (incl. DDX6, DGKQ, and NAB1) were flagged in a meta-GWAS study. Dysfunction in the gene encoding caveolin 1 interferes with the TGF-β pathway to suppress fibrosis, which has also been suspected [30].

Dense microsatellite analysis in Japanese SSc patients harboring the risk haplotype HLA-DPB1*13:01 demonstrated a probable association between a retinoid X receptor-beta (RXRB) variant and anti-topo I antibody. RXRB interferes with the fibrotic processes by suppressing them [31]. Recently, Shumnalieva et al. demonstrated deregulation of miR-21 and miR-29a in the serum of patients with SSc, which have pro- and antifibrotic effects, respectively [32]. It was confirmed that altered miRNA expression in the circulation or tissues is related to immune activation, vasculopathy, and fibrosis development in SSc patients.

2.8. Key Signaling Pathways Involved in Vascular Abnormalities

As has already been highlighted, vascular dysfunction in SSc focuses on the imbalance between the action of vasoconstrictors—most notably ET-1 and vasodilators, e.g., NO. Indeed, ET-1 appears to be increased in the skin, vasculature, kidneys, and lungs of SSc patients [8]. On the other hand, lower levels of NO are encountered in the vessels of SSc patients. TGF-β1 plays a pivotal regulatory role in this pathway, activating noncanonical (Smad-independent) pathways promoting myofibroblast activation, ECM synthesis, and ET-1 elevation [33]. As Ko et al. hypothesized, ET-1 appears to have an amplifying role in the bidirectional pathway of fibrosis and vasculopathy [8].

Conversely, a transcription factor expressed in ECs, known as Friend leukemia virus integration 1 (FLI1), seems to regulate skin fibrosis negatively. CXCL4 released by platelets suppresses the FLI1 pathway. Lower levels of FLI1 are associated with impaired vessel formation, fibrosis, and abnormal immune responses. Additionally, CXCL4 upregulates the expression of thrombospondin 1 expression and diminishes the action of VEGF [33].

Caveolin-1 forms invaginations resulting in the internalization of the TGF-β1 receptor and blocking TGF-β1-dependent signaling. Studies in mice have demonstrated that deletion of caveolin-1 results in impaired vascular tone regulation, the induction of spontaneous EndoMT, and skin and lung fibrosis. VEGF-A is also elevated in mesenchymal cells in the case of caveolin-1 deficiency [34].

A key element of fibrosis is EndoMT. This, in turn, is regulated through the action of various pathways, such as β-catenin, Wnt, Akt, Notch, phosphoinositide 3-kinase (PI3K), NF-kB, Sp1, and bone morphogenetic protein 4 (BMP-4) [8].

3. Microvascular Abnormalities in SSc

The microvasculature is part of the circulatory system composed of vessels <300 µm diameter, including arterioles, capillaries, and venules. Microvascular pathologies can manifest as vasculopathies or vasculitides. Vasculopathy generally refers to non-inflammatory vascular lesions (including those caused by immune complex deposition or intravascular thrombosis). At the same time, vasculitis is characterized by leukocytic infiltration (polymorphonuclear or mononuclear) and fibrinoid changes of the vascular wall. In SSc, microvascular abnormalities are typically noticed in the form of vasculopathy [1].

3.1. Microvascular Abnormalities Mechanisms

SSc microvascular disease is characterized by microvasculopathy, vasospasm, a procoagulant state with thrombosis and fibrin deposition, and defective angiogenesis. Endothelial cell injury is thought to be the initial event in developing vascular disease in SSc [35]. Factors involved in this injury include autoantibodies, infections (e.g., CMV), cytotoxic T-cells, and reactive oxygen species. Affected endothelial cells demonstrate endothelial cell activation with increased leukocyte adhesion molecules, cytoplasmic vacuolization, ballooning, cytoskeletal rearrangement, loosening of tight junctions, and apoptotic changes [35]. Histologically, affected vessels are characterized by neointimal lesions (proliferation of endothelial and smooth muscle cells and collagen deposition in the intima layer), adventitial fibrosis, perivascular mononuclear cell infiltration, and pericyte activation. The characteristic neointimal lesion likely results from an aberrant endothelial cell repair [36].

These altered microvascular endothelial cells have decreased expression of endothelial NO-synthase with reduced NO and increased ET-1 production. NO is a potent vasodilator, which inhibits platelet aggregation, smooth muscle cell proliferation, and cytokine-induced endothelial activation [37]. On the other hand, ET-1 is a vasoconstrictive factor that mediates smooth muscle cell proliferation, fibrosis, and inflammation. These alterations lead to a vasoconstrictive and procoagulant state. Chronic tissue hypoxia caused by this microvasculopathy, vasoconstriction, and microthrombosis triggers angiogenesis, which is, however, dysregulated due to differential expression of proangiogenic and angiogenic factors [36]. These new vessels are not well structured and are easily destroyed, leading to reduced capillaries in a given tissue area (capillary rarefaction) and capillary loss. Collectively, these mechanisms lead to significant microvascular damage and organ dysfunction [37].

3.2. Clinical Manifestations of Microvascular Abnormalities in Systemic Sclerosis

Raynaud phenomenon (RP) is a primary clinical manifestation of microvascular abnormalities and is present in most patients with SSc. RP in SSc is associated with structural abnormalities of the microvasculature and immune response. It is characterized by episodic vasospasm of the digital arteries in response to cold or emotional stress [38]. Distal body areas (fingers, toes, and occasionally the nose and ears) are the most affected and are more exposed to ambient temperature changes. This vasospasm leads to a distinctive sequence of color changes in the skin: pallor (due to ischemia), blue (due to hypoxia/deoxygenation), and red (due to reperfusion). These episodes are often accompanied by pain, tingling and numbness in the affected areas. Chronic and severe RP can result in persistent ischemia, leading to tissue damage and complications [38].

DUs and pitting scars are typical in SSc. DUs are a common and debilitating consequence of chronic microvascular compromise, particularly in SSc. They are defined as a denuded tissue area with a well-demarcated border involving loss of both the dermis and epidermis. These painful sores, typically located at the fingertips, result from prolonged ischemia and are difficult to heal. They are prone to infection, further complicating treatment and recovery, and they have the possibility of resulting in irreversible tissue loss, as well as other significant complications, including osteomyelitis, gangrene, and amputation. Pitting scars are another result of chronic ischemia and the healing of digital ulcers. These small depressions in the DUs and pitting scars highlight the severe impact of microvascular abnormalities on daily living and long-term health outcomes [38].

3.3. Diagnostic Techniques for Microvascular Abnormalities

Nailfold capillaroscopy (NC) is a non-invasive diagnostic tool that evaluates the morphology of capillaries using an optical magnification system, which is used primarily in connective tissue diseases like SSc [39]. This technique involves the microscopic examination of the capillaries at the nail fold bed. Abnormal capillaroscopic findings include enlarged capillaries, avascular areas, microhemorrhages, and capillary loss. These patterns provide insight into the severity and progression of microvascular damage. NC is particularly useful for diagnosing and monitoring SSc, offering a window into the extent of microvascular involvement and guiding therapeutic decisions [39].

Laser Doppler imaging and other modalities are useful in vascular abnormalities associated with SSc detection. Laser techniques are non-invasive tools that assess skin capillary perfusion, including laser Doppler flowmetry, Doppler imaging, and laser speckle contrast imaging. Laser Doppler imaging (LDI) measures blood flow by detecting the Doppler shift induced by laser light scattering of moving red blood cells [40]. LDI produces detailed maps of blood flow distribution, highlighting areas with reduced perfusion. This is especially useful for assessing the severity and extent of conditions like Raynaud's phenomenon and other microvascular disorders. The advantage of laser Doppler techniques is that they not only provide information about morphology but also on the dynamic behavior of microcirculation with different stimuli. This unique feature of LDI constitutes a promising approach, and more studies must be carried out to investigate its utility in clinical practice. Other modalities include laser speckle contrast imaging (LSCI), which measures the fluctuating granular pattern produced by laser light reflected on moving red blood cells. LSCI is a less time-consuming technique than NC and can be used to evaluate perfusion in the cutaneous microcirculation. However, more studies are needed to validate LSCI in SSc [40].

4. Macrovascular Abnormalities

4.1. Mechanisms of Macrovascular Involvement and Damage in SSc

While small vessel involvement (microvasculopathy) is often regarded as the hallmark of SSc, large vessels can also be widely impacted (macrovasculopathy) [41]. Over the past decade, a growing amount of evidence regarding the involvement of large vessels has been published [42]. Bertolino et al. further emphasize that several studies have demonstrated a greater macrovascular involvement in SSc compared to control subjects with similar cardiovascular risk factors [43].

Matucci-Cerinic et al. define large vessels as those with an internal diameter greater than 100 microns and note that involvement of the microvasculature often occurs in conjunction with distal pathology of the small vessels [44]. The involvement of both elastic arteries (i.e., carotid artery and aorta) and muscular arteries (i.e., brachial and ulnar arteries) are characteristic of SSc [42]. Lescoat et al. suggest that a similar mechanism may contribute to both micro- and macrovascular vasculopathy [45]. The mechanism of macrovascular involvement remains unknown and is likely multifactorial. Accelerated atherosclerosis and endothelial dysfunction are believed to be critical components in the pathogenesis [43].

Figure 1 presents the main pathophysiological mechanisms of vascular impairment in SSc patients.

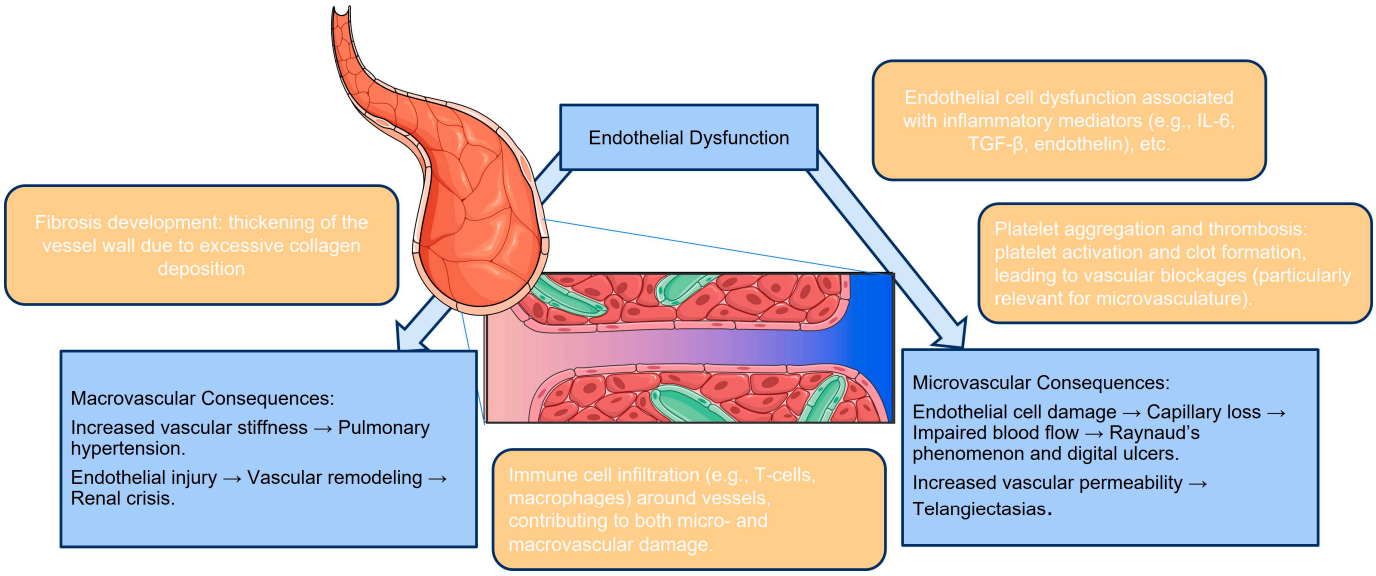

Figure 1. Pathophysiological mechanisms in micro- and macrovascular abnormalities in SSc patients. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons BY 4.0 (https://creativecommons.org/licenses/by/4.0/ (accessed on 10 September 2024)).

4.2. Clinical Manifestations of Macrovascular Abnormalities

Pulmonary arterial hypertension (PAH) is a common manifestation in patients with SSc [46], occurring in up to 12% of cases, and is often associated with severe complications [47], leading to significant morbidity and mortality [46]. This is further evidenced by Coghlan et al., who underline a considerable decrease in survival rates in SSc patients with PAH (56%), compared to (94%) in those without PAH [48]. This may partially be explained by the long asymptomatic period at the early disease phase and the non-specific symptoms of dyspnea and fatigue [47]. PAH comprises the two hallmarks of SSc, fibrogenesis and vasculopathy in the medium-sized pulmonary arteries, thus leading to obstruction of blood flow [41] and elevation of pulmonary artery pressure with subsequent right heart failure [49].

Ulnar artery occlusion (UAO) is considered an underestimated macrovascular manifestation of SSc, considering its eventual implication in DUs [50]. Supporting data on this is a study conducted by D'Alessandro et al., who assessed the macrovascular involvement in SSc using the resistance index (RI) and peak systolic velocity (PV) of ulnar and radial arteries by color Doppler sonography (CDUS) with spectral wave analysis (SWA). In total, 28% of those examined presented signs of UAOs [41]. Moreover, 83% of those with UAOs presented with DUs. D'Alessandro et al. emphasize the importance of UAO as a predictive indicator of DUs, considering the burden placed on patients. The radial artery is often spared in SSc vasculopathy, which is rather surprising considering the frequent implication of the ulnar artery [41].

Scleroderma renal crisis (SRC) is another form of SSc vascular disease. SRC affects around 5% of patients and is characterized by the sudden onset of severe hypertension due to the high renin state triggered by vascular injury. This may potentially be followed by acute renal failure [45].

4.3. Diagnostic Techniques for Macrovascular Abnormalities

The macrovascular involvement in SSc can be evaluated using various imaging techniques, as shown by D'Alessandro et al. One effective method is to measure the RI and PV of the radial and ulnar arteries using CDUS with SWA at the Guyon's canal of both wrists using a high-frequency probe in a controlled environment. The resistance index is defined as [(peak systolic velocity—peak diastolic velocity)/peak systolic velocity] [41].

Previous studies indicate that an RI greater than 0.70 may predict new DU development in SSc patients. However, findings suggest that healthy controls also exhibit an RI greater than 0.70, indicating that this parameter alone is insufficient for predicting DUs. Cut-off values of ulnar RI $\leq$ 0.82 and radial RI < 0.88 classified 94% of healthy controls, underscoring the need for combined diagnostic approaches [41].

Recent research by Schioppo et al. highlights the utility of Power Doppler Ultrasound (PDUS) in assessing both macro- and microvascular involvement. PDUS can identify UAO and reduced blood flow in the finger pulp, which are associated with capillary loss as measured by NVC [50]. Combining PDUS and NFC results by Lescoat et al. has shown strong associations with the primary digital manifestations of SSc, reflecting the severity of vasculopathy. This combined assessment approach helps identify patients with more advanced vascular pathology, offering better predictive capability for the risk of DUs than evaluating either macrovascular or microvascular impairment alone [45].

As already mentioned, the pathophysiology of vascular involvement in SSc includes dysregulation of immune cells from both innate and adaptive immunity, leading to the release of pro-inflammatory and profibrotic enzymes, such as those involved in the Wnt or TGF-β pathways. This dysregulation results in vascular damage and fibrosis. Taking these into account, UAO has been identified as a marker of severe vasculopathy and a predictor of DUs, particularly in patients with limited cutaneous systemic sclerosis (lcSSc) [45].

Bandini et al. demonstrated that abdominal ultrasound and CDUS can non-invasively assess splanchnic vessels, revealing morphological and functional differences in mesenteric arteries in SSc patients compared to healthy controls, suggesting "bowel vasculopathy" [51]. Additionally, renal arteries in SSc patients often show vascular damage without clinical symptoms, indicated by increased intrarenal stiffness but normal renal function. Hughes et al. described an overlap condition of SSc with Antineutrophil cytoplasmic autoantibodies (ANCAs), potentially representing a poor prognostic vascular phenotype [52].

Finally, CT is commonly used as an essential component of the diagnostic assessment of patients with suspected SSc-PAH. It allows for the visualization of associated ILD and excludes significant thromboembolic disease through CT Pulmonary Angiography (CTPA). Other features indicative of pulmonary hypertension (PH) can also be assessed using CTPA. Condliffe et al. proposed a combined index of the ratio of the diameter of the main pulmonary artery (dPA) and the diameter of the Adjacent Aorta (dAA), along with Tricuspid Gradient Measured at Echocardiography (TGECHO). It has been proven to have significant predictive value for mean Pulmonary Arterial Pressure (mPAP) in a diverse group of patients suspected to have PH [53]. However, the combined index has not been implemented widely in clinical practice.

5. Treatment Approaches in Vascular Abnormalities in SSc Patients

5.1. Pharmacological Treatments

Considering the multi-organ involvement, fibrosis, and vasculopathy in SSc, treatment should address these issues if they present [54]. Table 1 presents the current treatment options for SSc patients and their effectiveness for vascular abnormalities and complications [55–59].

In the initial stages of SSc, activation of the endothelium results in the upregulation of vasoactive mediators, such as endothelin 1. ET-1 receptor antagonists are therefore utilized to reverse this deleterious effect [60]. This class includes aniracetam with selective type A receptor action and bosentan and macitentan, which are dual antagonists at both type A and B receptors. In vivo studies in SSc patients demonstrated that aniracetam was associated with decreased pain, disability, and activity and the number of new DUs [33]. On the other hand, in vitro experiments showed reduced expression of mesenchymal markers in microvascular endothelial cells (MVECs) from SSc patients that were preincubated with bosentan or macitentan, pointing towards a potential mechanism to disrupt the EndoMT pathway [21].

Table 1. Treatment modalities for systemic sclerosis and their usefulness for improving vascular involvement.

Groups	Medications	Mechanism of Action	Useful for Vascular Complications of SSc
Vasodilators	Calcium channel blockers (e.g., Nifedipine, Amlodipine)	Relax blood vessels, improve blood flow	Yes, useful for Raynaud's phenomenon and digital ulcers
	Prostacyclin analogs (Prostanoids) (e.g., Iloprost, Epoprostenol, Treprostinil)	Vasodilation, platelet inhibition	Yes, used for severe Raynaud's phenomenon and pulmonary hypertension
	Endothelin receptor antagonists (e.g., Bosentan, Macitentan)	Block endothelin-mediated vasoconstriction	Yes, used for pulmonary arterial hypertension (PAH) and digital ulcers
	Phosphodiesterase Inhibitors (i.e., Sildenafil, Tadalafil)	Enhance nitric-oxide-mediated vasodilation	Yes, primarily for PAH treatment
ACE Inhibitors	Enalapril, Captopril	Inhibit angiotensin-converting enzyme, reduce blood pressure	Yes, useful in scleroderma renal crisis
Immunosuppressants	Mycophenolate mofetil, Cyclophosphamide	Suppress immune response to slow fibrosis progression	Limited, mainly for skin and lung involvement, not directly for vascular issues
Anti-Platelet Agents	Aspirin, Clopidogrel	Prevent blood clot formation	May provide some benefits for digital ulcers
Angiotensin II Receptor Blockers (ARBs)	Losartan, Valsartan	Block angiotensin II, reduce vascular resistance	Useful for controlling hypertension, limited for other vascular complications
Antifibrotic Agents	Nintedanib	Inhibit pathways leading to fibrosis	Primarily for lung fibrosis, limited direct vascular benefits
Anticoagulants	Warfarin	Prevent blood clot formation	Limited, mainly for secondary complications like thrombosis
Statins	Atorvastatin, Simvastatin	Improve endothelial function, reduce cholesterol levels	May have some vascular benefits, but not widely used specifically for SSc
Antifibrotic Immunomodulators	Tocilizumab (IL-6 inhibitor)	Block IL-6-mediated inflammation, slow fibrosis	Limited efficacy in direct vascular complications, useful in lung involvement
B-cell-Depleting Agents	Rituximab	Deplete B-cells, reduce autoantibody production	Limited direct vascular benefit, under investigation for broader effects
T-cell Modulators	Abatacept (CTLA-4 Ig)	Inhibit T-cell activation, reduce immune-mediated tissue damage	Currently, there is limited evidence for vascular benefits, mainly for skin and joint disease
Janus Kinase (JAK) Inhibitors	Tofacitinib, Baricitinib	Inhibit the JAK-STAT pathway, reducing immune signaling	Limited evidence for vascular benefit, mainly used for inflammation and fibrosis
TNF-alpha Inhibitors	Infliximab, Adalimumab	Block TNF-alpha, reducing inflammation	Not typically used for SSc due to lack of efficacy in vascular or fibrotic complications

Table 1. *Cont.*

Groups	Medications	Mechanism of Action	Useful for Vascular Complications of SSc
IL-1 Inhibitors	Anakinra (IL-1 receptor antagonist)	Block IL-1 signaling, reduce inflammation	Not commonly used for SSc vascular issues, limited data on efficacy
Anti-Th17 Agents	Secukinumab (IL-17 inhibitor)	Inhibit IL-17 activity, reduce inflammation	Minimal evidence for impact on vascular complications in SSc
Calcineurin Inhibitors	Tacrolimus, Cyclosporine	Suppress T-cell activation, reduce immune responses	Rarely used for SSc, limited benefit for vascular complications
PDGF receptor-α and -β, FGF receptor-1–3, and VEGFR-1–3 inhibitors	Nintedanib	Block signaling, improves spirometry parameters	Mainly for ILD
Botulinum toxin		Inhibits the release of acetylcholine from presynaptic nerve endings and reduces vascular smooth muscle contraction, thereby improving local circulation	Pain relief and promotes healing of limb ulcers.
Adipose tissue-derived mesenchymal stem cells		Healing of the DU and pain relief in some patients. It improves perioral fibrosis	Promise for treating SSc vascular involvement; healing digital ulcers, and pain relief in some patients. It improves perioral fibrosis

Other therapeutic options for SSc are phosphodiesterase inhibitors, which prevent cGMP hydrolysis by phosphodiesterase-5a and, therefore, prolong the activity of vasodilators, including NO [61]. In clinical practice, PDE-5A inhibitors have been shown to improve the frequency, duration, disability, and discomfort experienced in RP and promote the healing of DUs. Sildenafil has been applied in the treatment of SSc-PAH to improve cardiopulmonary function. According to a recent study, combined therapy of tadalafil plus ambrisentan for SSc-PAH demonstrated superior efficacy than single therapy with either agent [21].

Among the immunomodulator options, mycophenolate mofetil (MMF) inhibits inosine monophosphate dehydrogenase, thus suppressing the synthesis of guanosine nucleotides in lymphocytes and preventing cytokine release that would culminate in EC injury. A secondary effect of MMF is that it interferes with the glycosylation needed for the adhesion of lymphocytes and monocytes to ECs and downregulates the expression of adhesion molecules, hindering leukocyte recall to the vascular endothelium [21].

Cyclophosphamide (CYC) is an alkylating agent that affects the action of Tregs and lowers the levels of IFN-γ and IL-12 secretion. Although CYC is primarily used for SSc-related ILD, it has also exhibited a significant effect on vascular complications. In clinical practice, it demonstrated improved nail fold capillary patterns, increased serum levels of CCN1 and circulating EPCs, and reduced serum levels of endothelial damage markers [21].

Tocilizumab is a monoclonal antibody that interferes with the action of the IL-6 receptor, which has been implicated in the EC activation process and the fibroblast-to-myofibroblast differentiation process [33]. In a case report, the application of tocilizumab showed improvement in DUs, PAH, and ILD [62,63].

Treatments for vascular lesions currently focus on improving vascular endothelial function, reducing ischemia damage to visceral organs, and improving skin symptoms such as perioral sclerosis and fingertip ulcers. These treatments may target immunological or vasoactive substance pathways. It is important to remember, though, that various processes

indicate various treatment results. There is a great deal of individual variability in the clinical presentation of SSc. An evidence-based strategy is needed to address the various organ involvement requirements and provide the right medicine combinations [33].

5.2. Specific Treatment Options for SSc-Associated Conditions

5.2.1. Pulmonary Hypertension

Pulmonary hypertension has a devastating effect on the overall morbidity and mortality indices in SSc patients, making its early diagnosis and management a focal point in SSc therapy. The therapeutic options available for the treatment of SSc-PAH comprise four distinct groups of medications: endothelin receptor antagonists (ERAs), phosphodiesterase 5 (PDE5) inhibitors, prostacyclin analogs and receptor agonists, as well as soluble guanylate cyclase (sGC) stimulators [54]. Supportive therapy may also be required, and it involves the management of volume overload with diuretics, antiarrhythmic medications for atrial arrhythmias, and supplementation with oxygen for respiratory failure if indicated.

As Naranjo et al. noted, the suggested approach by the 6th World Symposium on Pulmonary Hypertension includes targeted therapy according to the identified risk of each patient based on a specialized risk stratification algorithm, most commonly the FPHN and REVEAL 2.0 risk systems. Achieving a low-risk level is the principal goal of the therapy, as it has been shown to improve mortality significantly. Monotherapy is generally inadequate, except for some select patients, and, usually, SSc patients with PAH classified as low-to-intermediate risk are offered combination therapy. In the group of patients identified as having high risk, a parenteral prostacyclin analog is added to the combination therapy. Patient response is evaluated initially within 1 to 3 months of therapy onset and, following that, at a 3- to 6-month interval [64].

Endothelin receptor antagonists (ERAs) block the endothelin pathway by interfering with endothelin receptor type A (ETA) and endothelin receptor type B (ETB), conferring a vasodilatory and antiproliferative effect [65]. The results of the BREATHE-1 trial proved bosentan's efficacy—an oral nonselective ETA/B antagonist—by showing ameliorated hemodynamic parameters and 6 min walk distance (6MWD) [65]. Accordingly, ARIES-1/ARIES-2 trials demonstrated that ambrisentan, preferentially targeting ETA, improved the 6MWD, although the effect was noted to be better in Idiopathic PAH (IPAH) patients when compared to SSc-PAH. In SSc patients, ambrisentan was able to slow disease progression and worsening of the clinical condition.

Macitentan, a newer nonselective ETA/B receptor antagonist, was studied in the SERAPHIN trial, where the results were consistent with a significant advantage in mortality and morbidity reduction over placebo. Macitentan has so far demonstrated superior efficacy in IPAH treatment when compared to the other ERAs, and as Bahi et al. reported, despite the lack of a dedicated trial, it is expected to have a similar effect in SSc-PAH [64,65]. A potential pitfall in the use of ERAs remains their toxicological profile, with the potential teratogenic effect limiting their use in pregnant women [54].

Prostacyclin analogs are also employed in SSc management. In SSc-PAH, prostacyclin levels are depleted, resulting in vasoconstriction and smooth muscle cell proliferation in the pulmonary artery and limiting cyclic adenosine monophosphate (cAMP) synthesis [65]. Epoprostenol, treprostinil, and iloprost are prostacyclin analogs, whereas selexipag is an agonist at the prostacyclin receptor. Epoprostenol is administered intravenously because of its short half-life, while intravenous and inhaled forms of iloprost exist. Additionally, treprostinil is manufactured in oral, intravenous, subcutaneous, and inhalational forms. Epoprostenol has demonstrated a beneficial effect on PAH by ameliorating exercise tolerance, hemodynamic function, and overall survival. Its widespread use is limited by its adverse effect profile, including infections, sepsis, and hypotension [64,65].

A randomized trial involving 470 PAH patients (including CTD-PAH) on continuous subcutaneous administration of treprostinil showed an improvement in the 6MWD, dyspnea indices, and hemodynamic parameters, even though the proportion of patients with SSc-PAH was limited [64]. Inhaled treprostinil has also demonstrated a potential advantage

for treating patients with combined SSc-PAH and SSc-ILD in a trial involving group 3 PH patients with SSc-ILD [65]. Similarly, intravenous infusion of iloprost improved 6MWD and reduced sPAP, while the inhaled form could have a role in acute PAH crisis management, as suggested by Jin et al. [66]. However, the narrow range of data available on inhaled prostacyclin analogs to treat the subgroup of SSc-specific PAH is quite problematic, and more trials are needed to clarify their effectiveness and potential limitations.

Selexipag is an oral prostacyclin receptor agonist that mediates pulmonary vasodilation. The subgroup analysis of the GRIPHON study in CTD-PAH patients demonstrated a significant reduction in the mortality and morbidity risk (−41%), while delaying disease progression and improving the cardiovascular parameters [66].

The nitric oxide pathway, PDE5 inhibitors, and guanylate cyclase agonists in SSc patients are also studied. In PAH, NO synthesis is downregulated, resulting in reduced cGMP levels. PDE5 inhibitors can mitigate this process, while guanylate cyclase agonists act on the soluble guanylate cyclase and elevate cGMP levels. The result is pulmonary vasodilation and inhibition of the proliferative processes [65].

Phosphodiesterase inhibitors, i.e., sildenafil, improved the 6MWD and the hemodynamic function (mPAP) in SUPER-1/SUPER-2 and PHIRST-1/PHIRST-2 studies both in PAH patients and in the subgroup of SSc-PAH cases. Additionally, PHIRST-1/PHIRST-2 reported a beneficial effect on the quality of life and delayed clinical worsening in the PAH population with similar results in CTD-PAH patients [64]. Tadalafil also showed improvement in the 6MWD, quality of life, and slower clinical worsening with the added effect of a longer-acting agent in IPAH. In SSc-PAH, combination therapy with tadalafil and ambrisentan, currently employed as a first-line option, seems to be especially effective. Although the evidence for using vardenafil in SSc-PAH is lacking, it has also shown similar benefits regarding improved hemodynamics and 6MWD [65].

The guanylate cyclase stimulator, Riociguat, acts on soluble guanylate cyclase (sGC), increasing cGMP levels. The PATENT-1/PATENT-2 trials demonstrated that riociguat has a beneficial effect in CTD-PAH, including in the SSc-PAH subgroup, by increasing the 6MWD and improving the functional class and the hemodynamic parameters.

Additionally, the RIVER study in PAH patients (14% were CTD-PAH patients) associated long-term riociguat therapy with improved RV function and decreased right heart size [65].

Multiple trials have demonstrated (e.g., the AMBITION trial) that initiating combination therapy early in the course of SSc-PAH with ERAs and PDE5 inhibitors significantly improves response and delays disease worsening [65]. In addition, Naranjo et al. illustrated that combination therapy in SSc-PAH patients without prior treatment increased the 6MWD, ameliorating the structure and function of the RV and the associated hemodynamic parameters. The follow-up ATPAHSS-O trial (SSc-PAH) additionally demonstrated improvement in pro-BNP levels.

Furthermore, the GRIPHON and SERAPHIN trials showed a reduction in mortality and morbidity following the addition of selexipag and macitentan to routine therapy, respectively [64]. As SSc-PAH has a particularly complex pathogenesis, future therapeutic approaches will likely include medications targeting different contributing pathways, e.g., a TGF-β signaling targeting agent, an immunomodulator, and a vasodilating agent [65].

Adjunct therapy for SSc includes the following. As SSc patients are predisposed to gastric antral vascular ectasias and ulcerative esophagitis, routine use of anticoagulation is not normally suggested unless specific clinical conditions require it. Additionally, the REVEAL Registry concluded that prolonged use of warfarin confers an unfavorable prognosis in SSc-PAH. Furthermore, although corticosteroids have benefitted survival and hemodynamics in other CTD-PAH patients, the results were not reproducible in SSc-PAH. Similarly, despite the broad usage of calcium channel blockers (CCBs) in RP, current recommendations do not promote their use in SSc-PAH due to their effect on esophageal motility [64].

Supplementation with iron has been suggested as a means to relieve hypoxic stress in PAH. However, the clinical trial of intravenous iron demonstrated no improvement in

the hemodynamic parameters and functional class by week 12. Conversely, the episodes of dyspnea were reduced, and a better quality of life was reported, most notably in iron-deficient patients with recurrent gastrointestinal bleeding and SSc-PAH [65].

5.2.2. Raynaud's Phenomenon

The dihydropyridine group of CCBs, with nifedipine being the prototype, is considered the first-line option in the treatment of RP. This is further supported by the results of a 2017 meta-analysis that evaluated the use of CCB in the treatment of primary and secondary RP. It was concluded that nifedipine, compared to placebo, reduced the frequency of the attacks in secondary RP by −4.19 and their severity, and the response was dose-dependent [67].

PDE5 inhibitors are classically regarded as second-line treatment in mild RP and as a second or third option (in combination therapy with prostacyclins) for severe RP. In 2013, a meta-analysis evaluated the effectiveness of sildenafil, tadalafil, and vardenafil by analyzing six RCT studies (244 patients, 92% of whom had SSc-related RP). The data from the meta-analysis demonstrated that sildenafil and tadalafil successfully lowered the frequency (−0.49), severity (−0.46 based on Raynaud condition score), and daily duration of the attacks (−14.62 min) [54].

In 2018, a randomized, n-of-1, double-blind trial conducted by Roustit et al. compared on-demand single doses of sildenafil prior to or during exposure to attack triggers versus placebo in patients with primary and secondary RP. The results demonstrated that, although there was a 90% probability that sildenafil was more effective compared to placebo, due to the high heterogeneity and relatively small effect size, on-demand PDE5 inhibitors were not, in fact, superior [68].

Current approaches suggest the use of prostacyclin analogs as rescue medication in cases of severe, refractory RP. The effectiveness of oral prostacyclin analogs, as well as selexipag, has not been demonstrated in secondary RP and, so far, only intravenous iloprost has yielded satisfactory therapeutic outcomes for SSc-related RP.

Alprostadil, a synthetic form of prostaglandin E1, has failed to show consistent benefit, with conflicting data arising from two trials. Ancillary treatments, such as topical application of nitrates (e.g., nitroglycerin and glyceryl trinitrate), demonstrated a beneficial effect (in a meta-analysis involving ~200 patients with secondary RP), with improved clinical status and hemodynamic function. Limitations include debilitating headaches and a contraindicated combination with a PDE5 inhibitor [54].

Aspirin, targeting platelet activation, might have a role in treating RP, and atorvastatin might be able to delay vascular injury. Pentoxifylline and fluoxetine might also benefit some patients, but the decision should be based on individual protocols. An advantageous effect in the severity and frequency of RP episodes was, indeed, demonstrated by a small, randomized trial comparing fluoxetine to nifedipine. Conversely, subset analysis of the RISE-SSc RCT showed no improvement in RP when comparing riociguat to placebo. Angiotensin II receptor type 1 blockers are regarded as a rescue option for treating mild RP in the case of nifedipine failure. However, their effectiveness is considered low [67].

5.2.3. Scleroderma Renal Crisis

Scleroderma renal crisis is associated with significant morbidity and comprises one out of the four main causes of death in SSc patients. As such, timely diagnosis and management are paramount [69]. Current guidelines on the management of SSc-associated renal crisis involve hospitalization and initiation of therapy with ACEIs; commonly, a short-acting agent is used (e.g., captopril). The goal is to achieve a 24 h reduction in systolic blood pressure by 20 mm Hg and to reach and maintain a blood pressure (BP) of 120/70 mm Hg by day 3 without hypotension. When the goal BP is met, the dose can be stabilized with a long-acting ACEI [70]. If BP remains uncontrolled with maximum acceptable doses of ACEI, adding a dihydropyridine calcium channel blocker may be useful. Due to their potential for stimulating the RAAS, diuretics should not be used unless volume control

is necessary. ACEIs, due to their vasodilatory effect on the efferent arteriole, can decrease renal function to the point where dialysis is unavoidable.

Therapy should continue while on dialysis, as per the guidelines, since almost half of the patients have been shown to partially recover within 3 to 18 months. ACEIs may mask the diagnosis of scleroderma renal crisis when used prior to an established acute crisis by maintaining a normal BP, leading to delayed diagnosis and increased risk of adverse outcomes, including death [70]. As the levels of circulating endothelin-1 have been reported to be elevated in SSc, ERAs can have a beneficial effect in managing acute SSc renal crisis.

Additionally, prostacyclins can have a role in rapidly lowering BP and improving renal blood flow. The recovery of renal function following a scleroderma renal crisis may take up to 2 years. Therefore, renal transplantation should not be considered before this time has passed [69,70].

5.2.4. Other Vascular Complications in Scleroderma

A multidisciplinary approach in the care of wounds (i.e., DUs) is indicated, especially on the occasion of large ulcers and strategies for wound care, e.g., the TIME algorithm (Tissue, Infection, Moisture, Edge) could have a beneficial effect [67]. Pain management and wound debridement should be employed as needed. As the risk of secondary infection is significant (up to two out of three patients), dressings incubated with iodine or silver nitrate can be used. Based on the local resistance patterns, empirical antibiotic therapy is another option when severe infection occurs.

Pharmacological treatment includes using a first-line CCB, followed by the addition of PDE5 inhibitors. Third-line treatment involves the utilization of prostacyclins, whereas bosentan and sympathectomy can both be considered prophylactically [67].

5.3. Non-Pharmacological Treatments for SSc

Therapeutic patient education should be pursued whenever applicable. It involves functionally re-educating the patient to avoid or modify certain habits to prevent and/or reduce disease exacerbation via lifestyle modification. General provisions include cold protection with gloves (incl. heated gloves), thermal clothing and space heaters, microtrauma protection, smoking cessation, and avoidance of vasoconstrictor drugs [70].

In the fight against exertional dyspnea, respiratory rehabilitation has shown significant advantages. Physical therapy and rehabilitation can be utilized symptomatically to increase regional blood flow and teach the patients to mobilize exercises for heat generation. Other techniques have also been suggested, including biofeedback, laser treatment, and acupuncture, but results have not been adequately satisfactory [54].

In summary, recent advancements have introduced novel agents and treatment strategies for addressing micro- and macrovascular abnormalities in SSc. These emerging therapies include endothelial progenitor cell therapy, antifibrotic drugs, and biologics targeting specific pathways implicated in vascular damage. Ongoing clinical trials are crucial for evaluating the safety and efficacy of these innovative treatments. Additionally, combination therapies and personalized medicine approaches are being explored to enhance therapeutic outcomes. Future research should focus on identifying biomarkers for early detection and monitoring response to treatment, ultimately aiming to improve the quality of life for patients with SSc [47]. However, despite recent advancements in our understanding of the underlying disrupted molecular pathways in SSc, there is still a great unmet medical need, as there is currently no treatment that addresses the fibrosis component of the illness. Novel studies reveal some inflammatory pathways that can be addressed by repurposing medications [71,72].

6. Conclusions

The management of micro- and macrovascular abnormalities in SSc remains a significant challenge due to the complex pathophysiology of the disease. Current therapeutic options, including pharmacological agents and biologics, have shown varying degrees of ef-

ficacy in mitigating vascular damage and improving patient outcomes. Emerging therapies, such as endothelial progenitor cell therapy and novel antifibrotic drugs, offer promising new avenues for treatment. Additionally, personalized medicine and combination therapies also potentially optimize treatment strategies. However, despite recent advancements in understanding the disrupted molecular pathways in SSc, a significant unmet medical need remains, as no treatment currently effectively targets the fibrotic component of the disease. Further research is needed to identify reliable biomarkers for early detection and accurately monitor therapeutic responses. By continuing to explore and develop targeted therapies, there is hope for significantly improving the quality of life and prognosis for patients with this complex autoimmune disease.

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