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THERAPEUTIC APPROACHES IN SYSTEMIC SCLEROSIS – WHAT'S OLD AND WHAT'S NEW? A LITERATURE REVIEW

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is an autoimmune disease that, because of its heterogeneity, presents clinicians with many therapeutic challenges. The hallmarks of its pathogenesis are vasculopathies, cutaneous or visceral fibrosis and the presence of scleroderma-related antibodies, however, the course of the disease is different in every case. Therefore it is important to adjust the treatment process individually to each patient's needs. In this manuscript we aim to describe options available for therapeutic management of SSc.
Materials and methods: An electronic literature search was performed using PubMed, Cochrane Library and Evidence-Based Medicine Reviews. Search terms included "systemic sclerosis", "methotrexate", "mycophenolate mofetil" "cyclophosphamide", "autologous hematopoietic stem cell transplantation", "tocilizumab", "nintedanib", "belimumab", "rituximab", "abatacept", "lenabasum" as keywords. The review focused on articles published in English from their inception until 2025.
Conclusions: However, the disease-modifying anti-rheumatic drugs are widely used in systemic sclerosis, currently the biological therapeutics are objects of dynamic researches due to their good benefit-risk ratio. Numerous biological drugs are implemented for alleviating the course of Interstitial Lung Disease as it remains main cause of death among SSc patients. Additionally, some clinical manifestations of SSc, including Raynaud phenomenon (RP) and Pulmonary Artery Hypertension (PAH) are treating rather symptomatically then causatively. We hope our manuscript contributed to better understanding of therapeutic approaches of systemic sclerosis.

KEYWORDS

Systemic Sclerosis, Biological Drugs, Disease-Modifying Anti-Rheumatic Drugs, Nintedanib, Tocilizumab, Rituximab

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Introduction and purpose:

Systemic sclerosis (SSc) is an autoimmune diseases of connective tissue affecting skin, vessels and various internal organs. Its' clinical course is heterogenous and depends on a few main pathophysiological events - vasculopathies, inflammation and fibroblasts producing excessive amount of extracellular matrix (Lepri et al., 2024). The prevalence is estimated from 3.1 per 100.000 to 144.5 per 100.000 (depending on ethnic groups). The disease manifests at any age and gender, but middle-aged women are the most prone to disease's development (Gumkowska-Sroka et al., 2024).

The main subtypes of SSc differ in the organ involvement, severity and mortality rate.

The limited cutaneous form (lcSSc)– formerly known as CREST syndrome – is characterized by skin thickening distally to the elbows and knees. It is the most common type of SSc constituting 60-80% of all patients (Lescoat et al., 2022) and is associated with mild clinical course and low mortality rate when compared to the diffuse form.

The diffuse cutaneous systemic sclerosis (dcSSc) is a subtype with a skin involvement of the face, trunk and proximal sites of the limbs. This subtype is characterized by early internal organs development and the 5-year survival rate of about 70% (Herrick et al., 2022).

Systemic sclerosis sine scleroderma (ssSSc) subset is rare and covers patients with sclerodermatous involvement of internal organs with concomitant absence of skin fibrosis (Kucharz & Kopeć-Mędrek, 2017). Noteworthy, patients with ssSSc are prone to progress to lcSSc or dcSSc. The research of Lescoat et al. (Lescoat et al., 2023), regarding patients with ssSSc who then progressed to the other subtypes, revealed the anti-Scl-70 antibodies as a risk factor for further skin involvement.

In 2013, American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed classification criteria containing major hallmarks of SSc – vasculopathies - presence of teleangiectasia, abnormal capillaries in capillaroscopy, cutaneous or visceral fibrosis - skin thickening of the fingers,

Interstitial Lung Disease or pulmonary arterial hypertension development, and the presence of scleroderma-related antibodies - anti-centromere, anti-topoisomerase 1, anti-Scl70, anti-RNA-polymerase 3 (van den Hoogen et al., 2013). The skin thickening of the fingers extending proximal to the metacarpophalangeal joints is sufficient criterion to make the diagnosis. In the absence of this symptom, other symptoms are evaluated using the point system – the diagnosis is established when patient receives at least 9 points.

Raynaud's syndrome is usually the first clinical manifestation of SSc and it precedes the skin thickening. The time interval between the manifestation of Raynaud's phenomenon (RP) and other symptoms' development is different in limited cutaneous form (about 5-10 years) and diffuse cutaneous form (1-2 years) (Volkmann et al., 2023). The nailfold capillaroscopy remains the golden standard in evaluating the alterations in the microcirculation and is used whether to confirm the diagnosis or to monitor progression of the disease. The capillaries in SSc are usually enlarged, dilated, abnormally shaped, with the presence of hemorrhages in the later stages (van den Hoogen et al., 2013). Importantly, Raynaud's phenomenon is associated with SSc when other disease's indicators are present - whether abnormal, scleroderma-specific nailfold capillaroscopy or with the presence of SSc-specific antibodies - anti-centromere, anti-topoisomerase I, anti-Scl, anti-RNA-polymerase (Smith et al., 2020).

Skin thickening and altered microcirculation contributes to the presence of digital ulcers and scars, resistant to treatment (Volkmann et al., 2023). Excessive collagen accumulation in the skin area near joints contributes to the reduction of motility.

The internal organs involvements are the reason for life-threatening complications. The Interstitial Lung Disease (ILD) remains the main cause of death among SSc patients, especially, when combined with pulmonary arterial hypertension (Distler et al., 2019). According to the literature data, even up to 65% patients present with SSc-caused lung abnormalities in high-resolution computed tomography (HRCT) (Hoffmann-Vold et al., 2019).

Gastrointestinal tract is the second most affected organ on the course of the disease – presenting involvement in almost 90% of patients with SSc with esophagus involved. Esophageal symptoms manifest as reflux disease and possible esophagitis (Volkmann et al., 2023). When lower gastrointestinal tract is involved, excessive fibrotic process leads to slow-paced gastrointestinal passage in intestines which contributes to the bacteria overgrowth resulting in malnutrition (Nassar et al., 2022).

Renal involvement of SSc is rarer than abovementioned organs, however can proceed dynamically and cause rapid deterioration of patient's clinical state. Scleroderma renal crisis (SRC) is a complication with a mortality rate of 20% at 6 months and is characterized by rapid renal insufficiency and malignant hypertension (Cole et al., 2023). Current implementation of ACE-I resulted in reduction of such complication.

Because of its heterogeneity, SSc presents clinicians with many therapeutic challenges. It is crucial to treat every case individually, considering the previous medical history, occurrence of organ complications, as well as potential benefits and complications of the treatment. In our manuscript we aimed to present both the SSc-treatment options that have been available for a while now, as well as some newer, more advanced therapeutic approaches.

Description of the state of knowledge

Disease-modifying anti-rheumatic drugs (DMARDs) are a class of medication with significant immunosuppressive and immunomodulatory effects, therefore are indicated in therapy of many autoimmune diseases, including SSc. They are generally classified in two groups - conventional DMARDs (cDMARDs) and biologic DMARDs (bDMARDs). cDMARDs commonly used in treatment for SSc are methotrexate (MTX), mycophenolate mofetil (MMF) and cyclophosphamide (CYC) (Benjamin et al., 2025).

MTX is a folic acid analogue that inhibits purine and pyrimidine synthesis, which eventually results in inhibition of the proliferation of potent cells (for example - immune system cells) (Papadimitriou et al., 2022). It was originally used in cancer therapy, yet it has also been found efficient in managing rheumatoid arthritis (RA) and other autoimmune diseases. MTX, through regulating cell survival signaling pathways, causes increased sensitization of fibroblasts and T-lymphocytes to apoptosis (Cronstein & Aune, 2020; Papadimitriou et al., 2022). The EULAR guidelines for treatment of SSc include MTX as a first-line therapeutic option for cutaneous sclerosis (Del Galdo et al., 2025)

CYC is a type of nitrogen mustard drug that is targeting intensively proliferating cells, therefore it has found its use in therapy of cancer and autoimmune diseases. Its effectiveness in SSc is mostly based on the suppression of helper and regulatory T cells, that results in declination of the levels of pro-inflammatory cytokines, like interleukin-2, interleukin-12, interferon γ, fibrogenic TGF-β or the immunoregulatory interleukin-10. It also causes a decrease in the number of active B-cells that correlates with lower production of antibodies (Ghiringhelli et al., 2004; Papadimitriou et al., 2022; Volkmann et al., 2023; Wachsmuth et al., n.d.)

The breakthrough randomized controlled trial (RCT) on CYC for SSc was the SLS 1 (Tashkin et al., 2006), conducted in patients suffering from SSc-related ILD to determine the outcome of oral CYC on lung function and health-related symptoms compared to placebo (Tashkin et al., 2006). After one year the results showed small but statistically significant benefits of oral CYC on lung function, cutaneous fibrosis, and the health-related quality of life (Tashkin et al., 2006).

Despite its efficacy, CYC is rarely used in the first-line of treatment for SSc, due to its severe adverse effects, such as leukopenia and thrombocytopenia (Papadimitriou et al., 2022; Volkmann et al., 2023). According to the EULAR guidelines, CYC as an early form of treatment should be mainly considered in cases of SSc-related progressive ILD (Del Galdo et al., 2025)

MMF is a prodrug of mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase (IMPDH) - the rate-limiting enzyme in de novo synthesis of guanosine nucleotides (Allison & Eugui, 2000). Its immunosuppressive effect is mostly based upon the particular dependence of T- and B-lymphocytes proliferation on this specific pathway (Allison & Eugui, 2000). MPA is also a known inductor of activated T-lymphocytes apoptosis (Allison & Eugui, 2000). Literature data shows that in patients suffering from SSc, who are treated with MMF the numbers of T-helper cells are significantly lower than in patients who did not receive any immunosuppressive treatment (Gernert et al., 2022). Moreover, it has been revealed that MMF-based treatment correlates with lower numbers of macrophages and myeloid dendritic cells in skin biopsies, as well as the reduction of the expression of the *CCL2* gene - an inflammatory chemokine (Hinchcliff et al., 2018).

MMF-based treatment may also reduce fibrosis, as MPA induces cytoskeletal dysfunction of fibroblasts, which inhibits their proliferation (Morath et al., 2008; Papadimitriou et al., 2022).

The significant RCT for MMF-based therapy in SSc was SLS 2 (Tashkin et al., 2016), which compared 24 months of MMF versus 12 months of oral CYC, followed by 12 months of placebo in patients with SSc-ILD. Over the 2-year course of the study, participants in both groups displayed significant improvements in lung function, lung imaging, and skin fibrosis, however MMF was much better tolerated and associated with less toxicity than CYC (Tashkin et al., 2016). Based on these findings, MMF is now generally considered as a first-line therapy for SSc in patients with ILD and diffuse cutaneous sclerosis (Bukiri & Volkmann, 2022; Kowalska-Kępczyńska, 2022; Volkmann et al., 2023).

Autologous hematopoietic stem cell transplantation (AHSCT) has been established as an effective method of treatment for SSc that, compared to aforementioned methods, may lead to the most spectacular improvements in cutaneous sclerosis and pulmonary fibrosis (Kowalska-Kępczyńska, 2022; van Laar et al., 2014; Zanin-Silva et al., 2021). AHSCT is mainly implemented in a second-line treatment for patients suffering from early diffuse cutaneous SSc or SSc-related ILD, who did not respond to immunosuppressive therapy (Kowalska-Kępczyńska, 2022; Pope et al., 2023). The efficiency of this method has encouraged clinicians to consider its application in a larger number of cases, even as an early form of treatment. Various high-quality RCTs, assessed in a meta-analysis and Cochrane review (Bruera et al., 2022) have shown superiority of AHSCT to intravenous CYC (Denton et al., 2024). However, given the fact that CYC is nowadays rarely used as first-line medication, there is still a great need for additional research in this topic (Bruera et al., 2022). In the pending UPSIDE clinical trial (NCT04464434) (Spierings et al., 2021) the use of AHSCT in a first-line therapy for dcSSc, is investigated versus intravenous CYC pulses followed by MMF (Spierings et al., 2021).

Even though AHSCT is very effective, it still remains an invasive and intensive medical procedure, associated with potential severe adverse events. Therefore, it is crucial to carefully assess anticipated benefits and possible toxicity in every patient's case individually (Bruera et al., 2022; Zanin-Silva et al., 2021). Before undergoing this procedure each patient must be comprehensively evaluated, especially for any signs of cardiovascular involvement, as most cases of transplant-related mortality in patients undergoing AHSCT are cardiac related (Farge et al., 2017; Zanin-Silva et al., 2021).

Biological drugs are widely used in autoimmune diseases. Due to their specificity to one biological target, they provide promising therapeutic effect with relatively low toxicity when compared to the DMARDS. Noteworthy, numerous biological drugs are administered in order to alleviate the course of ILD as it remains the main cause of death among SSc patients (Distler et al., 2019; Roofeh et al., 2021).

Tocilizumab (TCZ) is an IgG1 humanized anti-interleukin-6 (anti-IL-6) receptor monoclonal antibody. IL-6 is a chemokine secreted by myofibroblasts, M1 macrophages and B lymphocytes and has a pro-fibrotic effect, partially by triggering the polarization of M2 macrophages (Di Maggio et al., 2023). Its serum level is significantly elevated in patients with SSc, especially with dcSSc (Feghali et al., 1992). The increase of IL-6 concentration is a prognostic marker for disease's exacerbation and ILD development (Khanna et al., 2022). Tocilizumab's preventative effect in ILD was proven in randomized controlled trial whereas patients with dcSSc treated with TCZ achieved significantly better FVC preservation in the 48-week period of time when compared to the control groups (Khanna et al., 2016). Importantly, such effect was obtained when TCZ was administered in the early stages of the disease (Roofeh et al., 2021). Currently, TCZ is recommended as a first-line treatment in ILD accompanying both systemic sclerosis and mixed connective tissue disease and, in an addition to the first-line therapy, in SSc-associated skin fibrosis (Galdo et al., 2024; Johnson et al., 2024).

Nintedanib is a tyrosine kinase inhibitor which inhibits platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) receptors, and therefore, is proven to have anti-fibrotic, anti-inflammatory and vascular-remodeling effect (Distler et al., 2019). Its' clinical use in SSc is limited to SSc-caused ILD. SENSICS was a randomized, double-blind, placebo – controlled trial that confirmed nintedanib's slowing the decline of FVC among patients with SSc - caused ILD when compared to the placebo groups (Distler et al., 2019; Highland et al., 2021). Considering these results, EULAR's guidelines propose that nintedanib alone, or combined with MMF should be considered first-line treatment of SSc-induced ILD (Del Galdo et al., 2025). Importantly, the use of nintedanib might be burdened with gastrointestinal adverse effects with nausea and diarrhea being the most common (Kato et al., 2019). The addition of glucocorticosteroids helps with alleviating those symptoms.

Rituximab is a chimeric, anti-CD20 monoclonal antibody widely used in hematological malignancies numerous rheumatic diseases – inflammatory arthritis, myositis, ANCA-associated vasculitis or Susac syndrome (Johnson et al., 2024). The inactivation of lymphocytes B consecutively inhibits macrophage's differentiation and excessive fibrosis. This mechanism is the reason of rituximab's use in SSc (Di Maggio et al., 2023). Rituximab has been included in 2023 to the American College of Rheumatologist (ACR)/American College of Chest Physicians (CHEST) guidelines whether as a first-line treatment or as a treatment of progression of ILD accompanying systemic autoimmune rheumatic diseases (Johnson et al., 2024). Numerous researches prove that the addition of rituximab to the standard treatment scheme might be beneficial in treatment of resistant SSc-ILD, however current data are still scarce (Jang et al., 2025; Macrea et al., n.d.; Mankikian et al., 2023). On the other hand, according to Mankikan et al (Mankikian et al., 2023), the addition of rituximab to MMF in SSc-ILD treatment increases risk of viral infections, so the administration of RTX should be done with consideration and evaluation of the benefit-risk ratio.

Abatacept is cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein (CTLA-4-IgG). Its' potential use in SSc is explained by the researches reporting the pro-fibrotic role of cytotoxic CD4+ lymphocytes T in SSc (Khanna et al., 2020; Maehara et al., 2020). Additionally, skin biopsies of SSc patients containing cell infiltrates of lymphocytes T and macrophages prove the excessive activation of lymphocytes T during SSc (Khanna et al., 2020). The research of Khanna et al (Khanna et al., 2020) showed good tolerance of Abatacept among SSc patients, and visible decline of modified Rodnan Skin Score (mRSS) when compared to the control group. The research of Castellvi et al (Castellví et al., 2020) revealed alleviated morning stiffness, less swollen and tender joints and decreased mRSS score among patients treated additionally with abatacept. This research indicates potential use of Abatacept in SSc treatment, however further researches are still needed.

Belimumab is a human immunoglobulin G1λ monoclonal antibody that inhibits soluble B-lymphocyte stimulator (Neupane et al., 2023). It has been widely used in the treatment of systemic lupus erythematosus (SLE). Currently, there are discussions regarding its' clinical use in SSc patients. The double-blind, placebo – controlled pilot study (Gordon et al., 2018) aimed to assess the outcome of adding Belimumab to MMF therapy for dcSSc patients. However no significant difference in mRSS was noticed among experimental and control groups, the significant change in the signaling of B cells and fibrotic genes was revealed.

Lenabasum is a synthetic analog of THC-11-oic acid and works as the cannabinoid receptor type 2 (CB2) agonist, exerting anti-inflammatory and anti-fibrotic effect. The interest of its' use in SSc was probably caused by researches indicating that cannabinoids might play significant role in alleviating the SSc' progression by modulating the fibrogenesis (Gonzalez et al., 2012) or in alleviating the pain accompanying SSc-related ulcers (Cocchiara et al., 2019). The phase 2 of study of Spiera et al (Spiera et al., 2020) gathered patients receiving oral lenabasum as an addition to the immunosuppressive treatment or placebo and assessed their' clinical state using ACR/CRISS score. At 16 week, the lenabasum group received better ACR/CRISS score when compared to the placebo group which indicated lenabasum's positive role in clinical state's improvement. However, phase 3 of study did not confirm this assumption (Spiera et al., 2023). Undoubtedly, cannabinoids can provide beneficial effect for some SSc symptoms, however further researches are necessary to potentially include them to EULAR recommendations.

The management of SSc-related conditions

Microvascular damage and dysfunction of endothelial cells are hallmarks of SSc, leading to development of extensive and progressive vasculopathy (Romano et al., 2021; Volkmann et al., 2023; Zanin-Silva et al., 2021). Its most relevant clinical presentations are abnormal nailfold capillaries, RP, digital ulcers, erectile dysfunction, pulmonary arterial hypertension (PAH) or scleroderma renal crisis (SRC) (Romano et al., 2021; Volkmann et al., 2023)

RP is generally defined as peripheral vasospasm that leads to a fleeting change in color (erythema, cyanosis, and/or pallor) of digits, that may be accompanied by feeling of numbness. It is prompted directly by specific triggers, such as exposure to cold, rapid temperature fluctuations or stress (McMahan & Volkmann, 2020). RP is one of the first symptoms of SSc and it is observed in up to 95% of SSc-patients (Denton et al., 2024; McMahan & Volkmann, 2020; Zanin-Silva et al., 2021). About 50% of those patients experience serious ischemic complications, like digital ulceration and gangrene (Denton et al., 2024; McMahan & Volkmann, 2020; Nihtyanova et al., 2008; Zanin-Silva et al., 2021). Modern therapeutic strategies for vasculopathy in SSc concentrate mostly on improving symptoms, preventing loss of digital tissue and decreasing ischemic damage to internal organs (McMahan & Volkmann, 2020; Zanin-Silva et al., 2021).

Dihydropyridine calcium channel blockers (eg. amlodipine and nifedipine) are vasodilators generally considered the first-line medication in RP-therapy (Denton et al., 2024; Thompson & Pope, 2005). They also exhibit antioxidant properties (Allanore et al., 2004). Moreover, some RCTs suggest that patients receiving CCBs for RP are less likely to develop PAH in the course of their disease (Allanore et al., 2010; Denton et al., 2024). It may be due to their ability to decrease serum concentrations of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), which is considered a biologic marker for diagnosing early PAH in patients presenting no indication of heart failure (Allanore et al., 2003; Zanin-Silva et al., 2021)

Practically, PAH is a heterogenous group of conditions, which are commonly characterized by progressive vasculopathy of the pulmonary arteries and an elevated mean pulmonary arterial pressure (mPAP) (Haque et al., 2021). Those lead to an increase in pulmonary vascular resistance (PVR), which eventually results in increased right ventricular (RV) afterload with subsequent RV failure (Haque et al., 2021).

According to the global PAH prevalence study, PAH affects approximately 6.4% of SSc-patients (Rubio-Rivas et al., 2021). It is especially common in patients with anti-centromere antibodies, extensive telangiectasias and Th/To autoantibodies (8). Despite the advances in SSc-related PAH therapy, the condition is still associated with poor prognosis, with its 3-year survival rate oscillating around 52% (Lefèvre et al., 2013). Interestingly several studies have shown that the survival of patients with SSc-related PAH is relatively worse than in patients with idiopathic PAH, even though in SSc-PAH the pulmonary hemodynamics are usually less severe (Haque et al., 2021; McMahan & Volkmann, 2020; Volkmann et al., 2023). Due to its clinical relevance there is a special need for advancing SSc-related PAH therapy.

A class of medication, generally approved for SSc-related PAH treatment are endothelin-1 (ET-1) receptor antagonists. ET-1 is considered a crucial mediator in progression of vasculopathy in the course of SSc (Volkmann

et al., 2023; Zanin-Silva et al., 2021). This class of medication is also proven to be effective in therapy of digital ischemia, with bosentan preventing development of DU (Matucci-Cerinic et al., 2011) and ambrisentan, that not only stops the occurrence of new DU but also reduces the number of already existing ones (Denton et al., 2024; Parisi et al., 2013; Zanin-Silva et al., 2021). In SSc-associated PAH both of these medications significantly improve hemodynamic parameters (Iannone et al., 2008; Launay et al., 2010; Pan et al., 2019; Zanin-Silva et al., 2021). Moreover, bosentan restores the correct T-cells function, by interrupting the underlying changes in the T-cell/endothelium interplay, observed in SSc-PAH pathogenesis (Iannone et al., 2008).

Phosphodiesterase isoenzyme 5 inhibitors (PDE5i) (eg. sildenafil, tadalafil) are another class of vasodilatory drugs efficient in managing SSc-associated PAH (Barnes et al., 2019; Volkmann et al., 2023), which are also more and more commonly recognized as suitable for RP and DU therapy (even though there is still need for more research in this area) (Andrigueti et al., 2017; Denton et al., 2024; Impens et al., 2011; Kumar et al., 2013; Roustit et al., 2013; Volkmann et al., 2023). Moreover, combining PDE5i and ET-1 receptor antagonist in the first-line SSc-associated PAH treatment seems to give better results than any of these medications in monotherapy (Coghlan et al., 2017; Denton et al., 2024; Pestaña-Fernández et al., 2020; Volkmann et al., 2023; Zanin-Silva et al., 2021).

Another therapeutic option for RP, DU and SSc-PAH are prostaglandin I-2 (PGI-2) analogs, which are vasodilators with anti-aggregatory and anti-inflammatory properties (Zanin-Silva et al., 2021). In this class, most widely used are iloprost and epoprostenol, both showing similar efficacy, but intravenous iloprost having better stability and longer half-life (Milio et al., 2006; Stubbe et al., 2021; Zanin-Silva et al., 2021).

Similar medication is Selexipag, a selective prostacyclin receptor agonist that has been approved in treatment of SSc-associated PAH. In comparison to PGI-2 analogs it is characterised by better tolerance and longer half-life (Denton et al., 2017; Gaine et al., 2017; Sitbon et al., 2015; Zanin-Silva et al., 2021). It did not however perform well in RCT's concerning RP's treatment (Denton et al., 2017).

SRC, even though rare, is the most rapidly progressing and potentially fatal SSc vascular manifestation (Ahl et al., 2025). Affected patients usually present with sudden and severe increase in blood pressure, accompanied with acute oliguric kidney failure (Ahl et al., 2025; Zanatta et al., 2018). About 50% of patients demonstrate hemolytic microangiopathy characterized by anemia, thrombocytopenia, increased lactic acid dehydrogenase concentration and reduced haptoglobin levels (Zanatta et al., 2018). In the past SRC was considered the leading cause of SSc-related death, but over the last decade its prevalence has significantly declined - largely due to the introduction of angiotensin-converting enzyme inhibitors (ACEi) as the first-line of SRC-management (Ahl et al., 2025; Cole et al., 2023; Volkmann et al., 2023; Zanin-Silva et al., 2021). This form of treatment substantially increases survival and reduces the need for dialysis (Ahl et al., 2025; Volkmann et al., 2023; Zanin-Silva et al., 2021). Sadly, the attempts of using this class of medication as SRC-prophylactic did not give any promising results. Paradoxically, after the onset of SRC, previous exposure to ACEi was associated with worse outcomes and higher risk of death (Hudson et al., 2014).

Conclusions

SSc has a debilitating clinical course and the highest mortality rate of all rheumatoid diseases (Volkmann et al., 2023). Thus, researches regarding potential therapeutic approaches are of utmost importance. However DMARDs are relatively effective in SSc management, biological drugs are widely investigated due to their specificity and good benefits-risk ratio. The majority of newly administered drugs are applicable to alleviate the course of ILD as it remains the main reason of death. Currently, nintedanib is a breakthrough in the treatment of SSc-caused ILD and belongs to the EULAR recommendations. Our review presented biological drugs being currently under the consideration of including to the official guidelines. We described the most prevalent SSc-related conditions and presented current treatment options. The treatment schemes of SSc consist of both modifying the course of disease and alleviating the symptoms. We hope our manuscript contributed to better understanding of medical approaches of systemic sclerosis.

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Conceptualization: MJ and KO;
Methodology: KB and JK;
Software: HN and EO;
Check: PG and PK;
Formal analysis: DL;
Investigation: HN and PG;
Resources: JG and JK;
Data curation: KB
Writing – rough preparation: MJ and KO
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