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Editorial

Unveiling the Dual Benefits of Bosentan in Systemic Sclerosis: Risk and Relief

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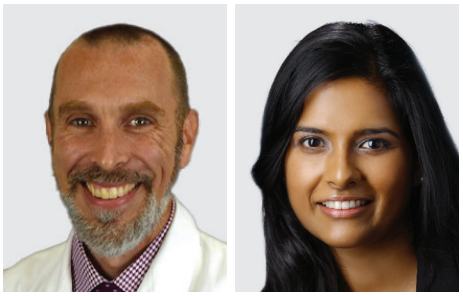

Digital ulcers (DUs) are a frequent and debilitating complication of systemic sclerosis (SSc), affecting approximately 50% to 70% of patients during their disease course.[1] These ischemic lesions result from severe microvascular dysfunction and impaired tissue perfusion inherent to the autoimmune vasculopathy underlying SSc pathogenesis.[2,3] The incidence of DUs in SSc is higher in individuals with the diffuse cutaneous subtype, advanced disease duration, or concurrent risk factors such as interstitial lung disease (ILD), elevated modified Rodnan skin score (mRSS) and a more severe disease course, with increased SSc-related mortality.[4] Despite advancements in disease management, DUs remain a significant cause of morbidity in SSc, leading to pain, disability, bone and soft tissue infections, and impaired quality of life.[1] The presence of SSc-associated DU has also been associated with an increased risk of pulmonary arterial hypertension (PAH),[4] reflecting overlapping pathways of microvascular dysfunction and endothelial injury, as well as shared epidemiologic factors, including diffuse cutaneous SSc, longer disease duration, and male sex.[5] Elevated levels of endothelin-1 (ET-1), a potent vasoconstrictor and pro-proliferative peptide, contribute to the concurrent development of DUs and PAH in SSc,[6] predicting both the future occurrence of DUs and incidence of PAH.[7] In 2011, a landmark double-blind, placebo-controlled clinical trial laid the foundation for bosentan, an oral endothelin receptor antagonist (ERA), in the prevention of DU in individuals with SSc.[8] However, establishing a definitive link between bosentan use for the treatment and prevention of DUs and its potential prophylactic efficacy in preventing PAH has remained an unanswered clinical conundrum.

In this issue of *The Journal of Rheumatology*, Cacciapaglia and colleagues draw from the Systemic Sclerosis Progression Investigation (SPRING) registry[9] to address this critical question.[10] In this retrospective analysis, 727 patients with SSc, without evidence of pulmonary hypertension (PH) on resting echocardiograms and receiving bosentan for DU prevention, demonstrated a reduced likelihood of developing incident PAH over a 2-year follow-up period. The study also revealed that risk factors associated with PAH development included the presence of DU, advancing age, increased mRSS, the presence of ILD, and acetylsalicylic acid use. The cohort, derived from the SPRING-SIR Italian registry encompassing 37 clinical centers, represents a real-world clinical population and stands as the largest cohort to date investigating the preventive effects of bosentan.[10]

As SSc is inherently characterized by endothelial dysfunction and vasculopathy,[11,12] it is not entirely surprising that there may be a link between different vascular manifestations, such as DU and PAH, and that bosentan may have prophylactic effects. Previous studies have shown that elevated ET-1 levels predict future development of DUs in patients with SSc,[6] and are also increased in the lungs of patients with SSc-associated PAH.[7] These studies cumulatively support elevated ET-1 levels as a key biomarker linked to vascular dysfunction in SSc, further highlighting its role in the pathogenesis of both DUs and PAH. Several studies have previously investigated the link between DUs and PAH, with conflicting results.[13] An Australian cohort study[14] demonstrated that history of DU was an independent risk factor for PAH development in patients with limited cutaneous SSc, whereas data from independent Italian[15] and Canadian[16] SSc registries found no difference in the incidence of PAH among individuals with or without a history of DUs.

Although the findings are certainly hypothesis generating, several methodologic issues must be considered, with appropriate tempering of any associated clinical implications. As an observational study based on a clinical cohort, the rigorous methodologies required to definitively exclude occult PH were not implemented, and as such, not all patients underwent right heart catheterization (RHC) at baseline or follow-up.[10] Patients

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were screened for incident PAH during a relatively short 2-year follow-up period using the 2-step DETECT algorithm,[17] relying on the echocardiography to assess for PH probability. Additionally, the fact that only 727 of the 1538 registry patients had complete data available for analysis suggests potential selection bias, as the included subset may not fully represent the broader population, possibly skewing the findings toward characteristics of those with higher clinical suspicion of PH. Further, since patients were recruited between 2016 and 2020, an earlier version of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines[18] was used to define PH, without conducting a sensitivity analysis to account for the updated lower threshold for mean pulmonary arterial pressure (mPAP) in the current definition of PH.[19]

Interestingly, the study by Cacciapaglia et al found that although bosentan exposure did not reduce the overall risk of PAH, it appeared to lower the risk of incident PH specifically in patients with SSc with a history of DUs, which was identified as an independent risk factor for PAH. If bosentan truly has a protective effect on PAH development in patients with SSc and DUs, an important question remains: Does this protective effect result from attenuation of vascular disease and prevention of PAH, or do patients still develop pulmonary vascular disease, with bosentan reducing the mPAP below the diagnostic threshold for PH? Since invasive hemodynamic data were unavailable, it is challenging to draw definitive conclusions. However, early studies of bosentan for PAH showed a modest average reduction in mPAP, ranging from 1.6 mmHg to 2.7 mmHg over 3-6 months.[20] Future prospective studies should describe RHC values to understand this critical mechanistic question.

The truth remains that there are no current evidence-based preventive treatments for PAH in patients with SSc. The authors should be complimented for studying this important question and demonstrating that there might be benefit to ERA use in high-risk patients with SSc. The updated ESC/ERS hemodynamic definition of PH[18] and associated lowering of the mPAP threshold to 21 mmHg has emphasized a focus on early detection and refinement of screening strategies in order to institute disease-modifying therapies. The EDITA study was a small randomized placebo-controlled trial of ambrisentan, a selective type A ERA, in patients with SSc and early pulmonary vascular disease (PVD), defined either as a mPAP of 21-24 or exercise-induced PH.[21] An open-label extension of this study demonstrated that no patients who were prescribed ambrisentan after the completion of the clinical trial (n = 19) developed manifest PAH (mPAP ≥ 25 mmHg), compared to a third of patients not prescribed ambrisentan (n = 12) who developed manifest PAH over a mean follow-up of 2.9 years.[21] Although this open-label extension enrolled a different population than the current study, Cacciapaglia et al[10] offer further evidence to support the concept that ERA use may be protective in patients with SSc at high risk of developing significant PVD. Ongoing prospective clinical trials of sildenafil and riociguat (ClinicalTrials.gov: NCT05339087) in patients with early PVD may clarify whether these medications can prevent progression of PH.[22]

The SSc community has made significant progress in the early detection and treatment of PAH. However, the focus must now shift toward strategies aimed at preventing this devastating and life-threatening complication of SSc. Urgent priority should be given to well-designed prospective observational studies and randomized controlled trials to establish evidence-based approaches for mitigating the development of SSc-PAH. The study by Cacciapaglia et al[10] introduces the concept of therapeutic synergy, highlighting that targeting specific vascular pathways, such as those implicated in both DUs and PAH, may yield dual benefits in managing the complex and multifactorial manifestations of SSc. Such an approach highlights the potential for integrated therapies to address overlapping vascular complications more effectively.

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COMPETING INTERESTS

The authors declare no conflicts of interest relevant to this article.

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