Is macitentan not a treatment option for digital ulcers in systemic sclerosis?

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Systemic sclerosis (SSc) is a chronic autoimmune and vascular disease resulting in extensive tissue fibrosis of the skin and various internal organs with unknown etiology. Although the entire pathogenesis of SSc still remains elusive, the canonical wisdom is that a complex network of cytokines, growth factors, chemokines, and cell adhesion molecules drives the three pathological components of this disease, including autoimmunity/inflammation, vasculopathy, and fibrosis, which co-operatively promote disease progression. The emergence of molecular targeting therapy has disclosed a hierarchical structure of complex molecular network in various diseases, including SSc (1-3). As a part of recent advances in the treatment of SSc, a dual endothelin receptor antagonist, bosentan, has provided strict evidence indicating a vital role of endothelins in the pathogenesis of SSc, especially its vascular aspect (4,5).

Endothelins are a family of potent vasoconstrictor peptides consisting of three isoforms, endothelin-1 (ET-1), -2, and -3, which bind to two G protein-coupled receptors, ETRA and ETRB. ET-1 is the predominant isoform and well-studied in various pathological conditions, especially vascular diseases. Besides a vasoconstrictive effect, ET-1 possesses a wide range of biological effects on different cell types. For instance, ET-1 induces a pro-angiogenic phenotype in endothelial cells and exerts a potent mitogenic action on fibroblasts and vascular smooth muscle cells. Also, ET-1 prolongs the survival of myofibroblasts by preventing apoptosis. In addition, ET-1 triggers the pathological inflammation by modulating the expression of cell adhesion molecules on endothelial cells and by promoting the production of interferon-γ from $CD4^+$ T cells. These proliferative, pro-fibrotic, and pro-inflammatory properties of ET-1 suggest its broad range of contribution to the development of SSc.

The expression profiles of ET-1 and its receptors are documented in the skin, lung, and kidney of SSc patients in comparison with closely matched healthy controls. In the lesional skin of early SSc, ET-1 and its receptors are abundantly expressed in small blood vessels of upper dermis, and the expression of its receptors is also enhanced in dermoepidermal junction (6). In the involved lung, ET-1 is detected in alveolar and bronchiolar epithelial cells, alveolar macrophages, capillaries, and fibroblasts, while the expression of its receptors is evident in alveolar and bronchiolar epithelial cells, bronchial smooth muscle cells, capillaries, and fibroblasts (7). In the kidney, ET-1 and its receptors are increased in glomeruli, interstitium, and vascular lesions at the onset of scleroderma renal crisis (SRC) (8). In agreement with these histological findings, circulating ET-1 levels are elevated in patients with diffuse skin sclerosis and pulmonary arterial hypertension (PAH) and patients at the onset of SRC (8,9). These data suggest that the blockade of ETRA and/or ETRB may modulate the natural course of cutaneous, pulmonary, and renal involvement associated with SSc.

There have been several reports on clinical trials and case series investigating the efficacy of bosentan for skin sclerosis, interstitial lung disease (ILD), PAH, SRC, and digital ulcers (DUs). At the time of writing, the prevention of new DUs is the only clinical effect strictly proved by the high-quality evidence based on randomized, prospective, placebo-controlled trials (4,5). With respect to the other symptoms, evidence is limited or shows no beneficial effect of bosentan. For instance, there are two clinical

studies (an open-label prospective study and an open-label cohort study) showing significant improvement of modified Rodnan total skin thickness score compared with baseline after 6-month treatment with bosentan (10,11), but its therapeutic effect on skin sclerosis has not been confirmed by case-control study. In case of SSc-associated ILD, bosentan failed to reduce the frequency of clinically important worsening in a randomized, prospective, placebo-controlled trial (12). Also, clinical data on SRC are not enough to draw a definitive conclusion, but bosentan was well tolerated and long-term outcomes were favourable compared with historical controls in a pilot open-label study with six cases (8). As well, in subanalysis of the BREATHE-1 study, a randomized, prospective, placebo-controlled trial of bosentan for severe PAH (WHO functional class III or IV), bosentan prevented deterioration in the walking distance in patients with SSc-associated PAH, but the quality of evidence was limited due to the small number of subjects (33 for bosentan and 14 for placebo in the subanalysis) (13). Importantly, a couple of preliminary studies have revealed that bosentan may prevent the development of SSc-associated PAH (14). Overall, bosentan is likely to have a broad spectrum of disease-modifying effects on vascular complications of SSc.

Although bosentan is useful for the prevention of DUs in SSc, it is not tolerable in a certain subset of patients due to its hepatotoxicity. Also, bosentan is not applicable to patients under the treatment with calcineurin inhibitors, treatment option for SSc patients with severe inflammatory and fibrotic conditions. Macitentan is a dual endothelin receptor antagonist discovered as a derivative of bosentan through computer-aided drug design. Macitentan shows excellent pharmacokinetic properties, such as sustained receptor binding ability and enhanced tissue distribution compared with bosentan, and no demonstrable increase in the risk of hepatotoxicity. In addition, macitentan can be administered in patients treated with calcineurin inhibitors. It is already approved as a therapeutic drug for PAH and widely used (15). Given the efficacy of bosentan on the prevention of DUs, macitentan was theoretically expected to elicit a similar or better beneficial effect on DUs in SSc patients.

Recently, the results of the DUAL-1 and DUAL-2 studies, randomized, prospective, placebo-controlled trials of macitentan for SSc-related DUs, have been reported (16). These studies were conducted with the same inclusion criteria and protocols as the RAPIDS-2 study with minor modifications. Contrary to expectations, the DUAL studies did not prove the beneficial effect of macitentan on SSc-related DUs. However, there are several important issues to consider when we compare the results of the DUAL studies and the RAPIDS-2 study.

Closely looking at the results of the DUAL studies and the RAPDS-2 study, it is noted that the number of new DUs during the observational period is basically much smaller in the DUAL studies than in the RAPIDS-2 study. In the placebo groups, the number of new DUs at 16 weeks was 0.85 (95% CI, 0.59–1.23) in DUAL-1 and 1.21 (0.87–1.67) in DUAL-2, while 2.7 (1.7–3.7) at 24 weeks in RAPIDS-2. Furthermore, patients with ≥4 DUs developed 1.16 (0.64–2.13) and 1.79 (1.16–2.76) new DUs and patients with <4 DUs developed 0.64 (0.41–1.00) and 0.78 (0.50–1.24) new DUs at 16 weeks in the placebo groups of DUAL-1 and DUAL-2, respectively. On the other hand, patients with ≥4 DUs developed 4.4 (2.8–6.1) new DUs and patients with <4 DUs developed 1.9 (1.3–2.5) new DUs at 24 weeks in the placebo group of RAPIDS-2. Given that the severity of DUs seems to be similar between the DUAL studies and the RAPIDS-2 study (the average number of DUs at baseline; 3.4±2.4 in all the patients of DUAL-1, 3.5±2.2 in all the patients of DUAL-2, 3.6±3.3 in the placebo group of RAPIDS-2, 3.7±4.4 in the bosentan group of RAPIDS-2), the decreased number of new DUs in the placebo groups of the DUAL studies suggests that some factors affecting the development of new DUs may be changed during the recent 10 years (study period: from October 2003 to May 2005 in RAPIDS-2, patient recruitment period: from January 2012 to November 2013 in DUAL-1, from February 2012 to February 2014 in DUAL-2).

One of the candidate factors is the education of patients as well as clinicians and nurses for the management of DUs. In the recent decade, especially after the emergence of bosentan, DUs have caught much attention as a critical complication affecting the morbidity of SSc, and the management of DUs is remarkably improved. For instance, there are more sessions than before dealing with SSc-associated DUs in the annual meetings of American College of Rheumatology and European League against Rheumatism. Furthermore, patients can access to the general information of DU management more easily than before through social media, allowing patients to communicate with each other and share the beneficial information. Probably, these factors strengthen the Hawthorne effect, possibly decreasing the number of new DUs in the DUAL studies compared with the RAPIDS-2 study.

Also, the wide-spread use of bosentan against SSc-related DUs potentially alters patient population enrolled in the clinical trials for this complication. As described above, the number of DUs at baseline is almost the same between the DUAL studies and the RAPIDS-2 study. However, the values of standard deviation are smaller in patients enrolled in the DUAL studies, suggesting that the proportion of SSc patients with severe DUs may be lower in the DUAL studies than in the RAPIDS-2 study. As reported in the RAPIDS-2 study, the preventive effect of bosentan on new DUs is higher in patients with ≥4 DUs than in patients with <4 DUs. Therefore, the registration of patients with severe DUs was ideal to clearly evaluate the preventive effect of macitentan on DUs. However, the wide-spread use of bosentan, as well as prostanoids and phosphodiesterase-5 inhibitors, might decrease the number of SSc patients with severe DUs who met the inclusion criteria of the DUAL studies, such as "no history of phosphodiesterase-5 inhibitor treatment" and "untreated with prostanoids and endothelin receptor antagonists within 3 months prior to screening". This may be a potential limitation of the patient recruitment in the DUAL studies.

Alternatively, the education of clinicians for the early diagnosis of SSc may promote the enrollment of SSc patients with milder clinical features in the DUAL studies. In the 2000s, the importance of early diagnosis of SSc had attracted much attention, and preliminary criteria for the very early diagnosis of SSc was eventually established in 2011 (17). It is speculated that this has promoted the early diagnosis of SSc. As well, the rapid growth of social media allows patients to access these information, possibly increasing the opportunity for patients to suspect themselves of having SSc. Consistent with this idea, time from first occurrence of DUs to randomisation is shorter in the DUAL studies [median (range): 4.5 (0.1–37.1) years in DUAL1 and 5.3 (0.1–55.0) years in DUAL2] than in the RAPIDS-2 study (6.4±7.1 years in placebo group, 7.4±8.7 years in bosentan group). Since vascular complications generally progress along with disease duration, patients in the DUAL studies might have milder vascular changes than those in the RAPIDS-2 study.

Although the DUAL studies did not support the use of macitentan for SSc-related DUs, we need to notice that these clinical trials were conducted to assess the effect of macitentan on SSc-related DUs in the absence of other drugs acting on vasculature, such as prostanoids and phosphodiesterase-5 inhibitors. As previously reported, bosentan normalizes the pathological property of SSc endothelial cells and the circulating levels of various disease-related molecules (18,19). In addition, bosentan counteracts the anti-angiogenic effects of SSc sera on dermal microvascular endothelial cells *in vitro* (20). Consistent with these findings, bosentan improves nailfold capillary changes (21). Furthermore, contrary to the results of the RAPIDS studies, there are many case reports showing that bosentan seems to accelerate the healing of refractory skin ulcers in SSc patients (22). A possible hypothesis explaining this discrepancy is that bosentan is mostly used in combination with other vasoactive drugs and topical therapies in daily clinical practice, some of which are prohibited in the RAPIDS studies. Supporting this idea, prostanoids do not show any effect on nailfold capillary changes, but the combination therapy of bosentan with prostanoids promotes the formation of new vasculature to a greater extent than the monotherapy of bosentan (21,23,24), suggesting that bosentan may render SSc endothelial cells responsive to prostanoids. Importantly, a possible synergy of bosentan with prostanoids is also implied in SSc-associated PAH (25). Therefore, we still cannot deny the possibility that macitentan possesses some beneficial effect on vascular complications of SSc beyond the results of the DUAL studies when used in combination with other vasoactive drugs.

Recent studies have identified some disease-modifying drugs for SSc, including tocilizumab, rituximab, and fresolimumab, in addition to bosentan (1-3). Reflecting the heterogeneity of this disease, the clinical efficacy of these drugs is basically variable in individual cases and at best partial in most cases. Since SSc disease process is driven by a complex network of various molecules, the combination of some molecular targeting therapies is theoretically appropriate to obtain a maximal therapeutic effect. From this point of view, even though the DUAL studies did not prove the preventive effect of macitentan on new DUs as a monotherapy, there is still possibility that its combination therapy with other disease-modifying drugs may exert a significant therapeutic effect on DUs and/or other symptoms considering the critical role of ET-1 in SSc development. Therefore, we should carefully interpret the results of the DUAL studies and keep in mind the potential of endothelin receptor antagonists to inhibit a critical piece of the complex pathological network driving SSc pathogenesis.

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Footnote

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