Selexipag may be effective in inducing digital ulcer healing in patients with systemic sclerosis

Sirs,

Fingertip digital ulcers (DUs) may complicate the course of systemic sclerosis (SSc) in about half of the patients. This event leads to a significant deterioration of the patient's quality of life, since it may be associated with severe pain and difficulty in performing the simplest daily living activities (1). Management of DUs is challenging and requires a complex treatment including both systemic and local therapies. Systemic treatment of DUs is focused on bosentan as prevention of ulcers recurrence, and on vasodilatatory agents. Among these, only phosphodiesterase 5 inhibitors (PDE5is) and intravenous iloprost reached a sufficient level of evidence to be recommended for this purpose (2). Iloprost infusion (0.5–2 ng/kg/min for 3–5 consecutive days) is largely used in this clinical setting, namely when any alternative therapy failed. However, intravenous administration often presents a few hurdles including difficulties in venous access, high costs for hospitalisation, and time lost from work productivity of patients.

We report the results of an open observational study conducted in six patients with SSc, who met the 2013 classification criteria of ACR/EULAR for this disease, in whom healing of DUs was achieved after treatment with selexipag, an oral, selective IP prostacyclin receptor agonist (3). Selexipag therapy was motivated by the failure of standard therapy (calcium-channel blockers, bosentan, sildenafil and intravenous prostanoids) to achieve DU healing, and by the difficulties in finding an adequate venous access for iloprost infusion. This off label use of the drug was approved by hospital officials, in accordance with the local rules for rare diseases. Informed consent for the treatment was obtained by all the enrolled patients.

In the six cases, healing of all the DUs was reached after 3–6 months of therapy with selexipag (2400–3000 mgr per day). A contemporary complete resolution of DU related-pain was recorded in all the patients, while a substantial improvement of Raynaud's phenomenon (RP) burden was observed in four out of five patients. The main demographic and clinical data of the patients are detailed in Table I.

Selexipag exerts an agonist effect of prostacyclin IP receptor inducing a potent vasodilatation. In view of this effect, selexipag has been tested with positive results, and then approved as monotherapy for the treatment of pulmonary arterial hypertension (PAH), also associated with systemic autoimmune diseases such as SSc (4). Furthermore, on the basis of the results that have been achieved on the efficacy of selexipag in association with endothelin receptor antagonists (ERAs) and PDE5is, this drug has recently been approved even in combination therapy in well-defined subsets of patients with PAH (5). Conversely, in a randomized controlled trial (RCT), selexipag failed to demonstrate efficacy on SSc-related RP (6). Up to now few inconclusive data have been published on the effect of selexipag on the treatment of DUs, even though DU healing was recorded in all the three patients included in the active arm of the above-mentioned RCT (6).

In the present small series of patients, the addition of oral selexipag therapy has shown to be effective in inducing DU healing in patients with SSc in whom standard therapy was not effective. We are aware that this is an open observational study on a very limited number of patients. However, these preliminary results may pave the way for a more extensive exploration of this potential new therapeutic indication of selexipag in SSc.

In conclusion, the efficacy of selexipag on SSc DUs suggests a wider utilisation other than pulmonary hypertension.

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Table I. Demographic and clinical data of the patients with SSc-related DUs treated with selexipag.

Pt	Age (years)	SSc variant	Disease duration (years)	Observation time	DUs duration before selexipag (months)	n. of DUs	Likert Pain Scale	RCS	Concomitant therapies and relative duration (months)
1	45	dcSSc	12	T0	48	2	4	9	MMF (48),Tocilizumab (27)
				T1		0	0	0	Bosentan (108)
				T2		0	0	0	Sildenafil (84)
2	65	dcSSc	20	T0	108	3	4	9	Bosentan (90)
				T1		0	0	5	Sildenafil (72)
				T2		0	0	2	
3	40	dcSSc	2	T0	12	7	6	7	Tocilizumab (2)
				T1		6	3	2	Macitentan (3)
				T2		0	0	2	ASA (9)
4	29	lcSSc	3	T0	12	4	6	8	Bosentan (8)
				T1		1	2	3	Sildenafil (3), ASA (8)
				T2		0	0	3	
5	33	dcSSc	5	T0	36	3	5	6	MTX (24)
				T1		1	2	4	Bosentan (24), Sildenafil (20)
				T2		0	0	4	ASA (36)
6	45	dcSSc	6	T0	24	4	5	6	MMF (18)
				T1		2	2	2	Sildenafil (24),
				T2		0	0	2	ASA (36)

Pt: patient; dcSSc and lcSSc: diffuse cutaneous and limited cutaneous systemic sclerosis; T0, T1, T2: observation times at the beginning, after three months, and after six months of selexipag therapy, respectively; DUs: digital ulcers; RCS: Raynaud's Condition Score, a Likert scale ranging from 0 to 10 for patient's self-evaluation of the mean difficulty due to his/her Raynaud's condition in the last two weeks; MMF: mycofenolate mofetil; ASA: acetyl salicylic acid (100 mg per day); MTX: methotrexate.

Letters to the Editors

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