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Letter to the Editor |
Matters arising from published papers

British Society for Rheumatology RHEUMATOLOGY OXFORD

Comment on: Long-term effects of selexipag in SSc-associated digital ulcers: a case-control multicentre observational study: reply

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Dear Editor, We thank Dr Wuttge for his interest in our study [1] and for the opportunity to clarify the points raised.

Upon rechecking the original dataset, we identified a typographical error in Table 2 regarding the number of patients receiving triple vasoactive therapy in the selexipag group, which was incorrectly reported as 4 instead of 3. Importantly, the reported percentages were correct, and this error does not reflect any inaccuracy in the underlying data. The table has been corrected accordingly. Following this correction, we reran all relevant statistical analyses, including between-group comparisons and multivariable models. Specifically, we re-performed Fisher's exact tests for all categorical variables, including combination therapy distribution, smoking status, and other baseline characteristics. For variables with multiple categories (such as smoking status and combination therapy), we conducted both overall comparisons and separate binary Fisher's exact tests comparing each category individually against its reference group (e.g. each smoking category *vs* non-smokers; each combination therapy level *vs* no therapy). This approach provides both an overall assessment and a more granular evaluation of potential differences in each specific category between treatment groups. These analyses fully confirmed the original results and conclusions, which are now documented in Supplementary Tables S1 and S2, provided with this reply.

Regarding the concern about potential confounding factors, we agree that differences in concomitant vasoactive therapy and smoking status deserve careful consideration, even though not statistically significant. Dr Wuttge referred to a retrospective study of a small group of SSc patients with DUs who were treated with bosentan to prevent DUs. Active smokers had a significantly higher rate of complications in their medical history before starting bosentan treatment, but no data were reported on the effect of smoking on DU healing afterwards [2]. Furthermore, the literature about the influence of smoking on DU healing has yielded conflicting results, and robust adverse effects of smoking on the progression of SSc cutaneous manifestations have not been demonstrated [3–5]. To address these concerns, we therefore conducted additional multivariable Cox regression analyses adjusting for combination therapy and baseline digital ulcer count. The Cox regression model included the following covariates: treatment group (selexipag *vs* iloprost), combination vasoactive therapy (monotherapy, dual, triple), active smoking, and baseline DU count. As 46 events were observed, we included 6 covariates in the multivariable model (Fig. 1). Importantly, after adjustment for these covariates, treatment with selexipag remained independently associated with faster DU healing (HR 6.962, 95% CI, 3.230–15.006, $P < 0.001$), while different combinations of vasoactive drugs did not (Fig. 1). Thus, the main conclusions of our study remain unchanged [1].

Finally, we appreciate the opportunity to clarify funding aspects. Selexipag was prescribed under off-label compassionate use, approved by hospital authorities in accordance with Italian law 648/96. Treatment costs were conditionally covered by regional healthcare systems, and no pharmaceutical company provided the drug or financial support for this study.

We thank Dr Wuttge for his comments, which allowed us to further verify and clarify our analyses. We remain confident that our findings support a potential role for selexipag in refractory

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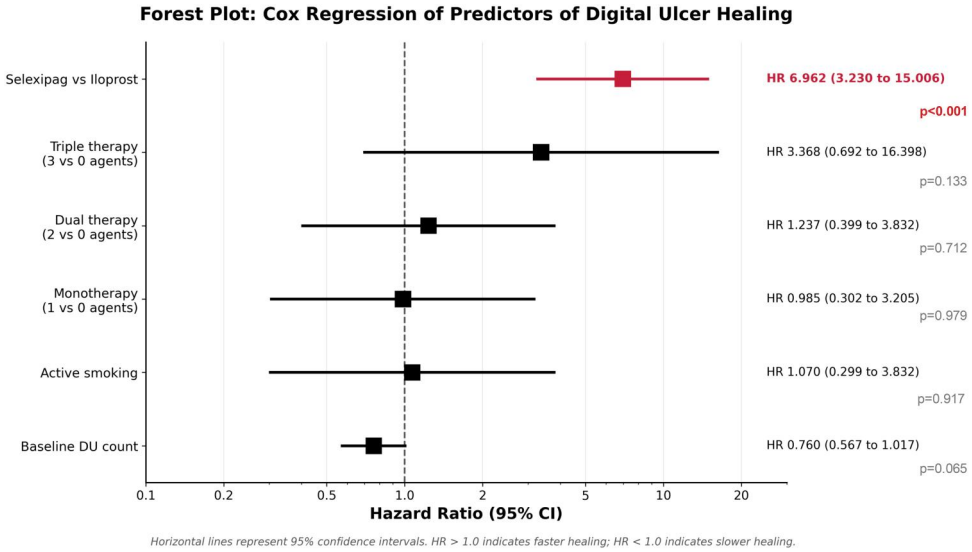

Figure 1 Multivariable Cox regression for digital ulcer healing. Forest plot from Cox regression analysis of digital ulcer healing predictors. Selexipag versus iloprost (red square) shows significantly faster healing with HR 6.962 (95% CI, 3.230–15.006, $P < 0.001$). Triple therapy shows HR 3.368 (95% CI, 0.692–16.398, $P = 0.133$), dual therapy HR 1.237 (95% CI, 0.399–3.832, $P = 0.712$), and monotherapy HR 0.985 (95% CI, 0.302–3.205, $P = 0.979$), all non-significant. Baseline DU count shows HR 0.760 (95% CI, 0.567–1.017, $P = 0.065$). Red indicates statistical significance ($P < 0.05$); black indicates non-significance

systemic sclerosis—associated digital ulcers, while recognizing, as already specified in the original manuscript, that prospective randomized studies are warranted.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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