

OP0119 BOSENTAN REDUCES THE NUMBER OF NEW DIGITAL ULCERS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background: Digital ulcers (DU) are an important source of disease-related morbidity in SSc for which there are no effective oral therapies. The aetiology of DUs in systemic sclerosis (SSc) is unclear, but endothelin is implicated as a key mediator of vasculopathy.

Objectives: We report a large randomized, placebo-controlled clinical trial (RCT) with bosentan, a dual endothelin receptor antagonist, in which we sought to confirm the reduction in number of new DUs observed in a previous trial in 122 patients [1] and to evaluate potential effects on healing.

Methods: Study eligibility included a diagnosis of SSc and at least one recent active DU. In patients with more than one active DU, a "cardinal ulcer" was identified based on location, clinical impact and amenability to healing. Patients received bosentan at 62.5 mg bid for 4 weeks then 125 mg bid for 20 to 32 weeks or placebo (PBO), in 1:1 double-blinded randomization. DUs were assessed at 4 weekly intervals. Co-primary endpoints were time to complete healing of the cardinal ulcer and the total number of new DUs observed up to week 24. Secondary endpoints included SHAQ-DI, safety and tolerability.

Results: The 188 patients studied in 41 centers in North America and Europe were well balanced between bosentan and PBO by age, gender, SSc classification, smoking history and concomitant medications. Total number of new ulcers per patient up to 24 weeks was 1.9 ± 0.2 on bosentan versus 2.7 ± 0.3 on PBO ($p = 0.035$, Pitman permutation). The reduction was more pronounced in patients with more than 3 active digital ulcers at baseline. The effect on healing was comparable between bosentan and PBO, 50% of patients in each group showed persistence of the cardinal ulcer at 24 weeks. Bosentan therapy was associated with improved hand function. SHAQ dressing improvement was significant for bosentan over PBO at 24 weeks ($p=0.033$) and trended in favour of drug for eating at 24 weeks ($p= 0.098$). SHAQ Visual Analogue Scales improved on bosentan for pain at 12 weeks ($p=0.034$). SAEs were uncommon. ALT/AST > 3X ULN was more frequent on bosentan (10.5%) than PBO (1.1%).

Conclusion: This second large RCT confirms that bosentan reduces the number of new DUs in patients with SSc and that this effect is associated with reduced pain and improved hand function. Bosentan therapy does not appear to facilitate healing of active DUs.

References: [1] Korn JH. Arthritis Rheum 2004; 50: 3985-3993.