# INITIAL EVIDENCE IN THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE) TREATMENT WITH BOSENTAN

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## ABSTRACT

Thromboangiitis obliterans (TAO) is a vascular disease that affects small and medium-sized arteries and veins of both upper and lower extremities. Distal ischaemic lesions and digital necrotic ulcers, as well as major amputation rates, among these patients are not negligible. So far, no treatment option has been demonstrated to be completely effective for this disease. Endothelin-1 (ET-1) has been increasingly associated to vascular damage. Furthermore, elevated levels of ET-1 have been proved in TAO patients. Thus, ET-1 receptor antagonists may be considered as a treatment option in this disease.

Consistently, initial results from open-label studies or case reports show promising efficacy of bosentan for treatment and prevention of digital ulcers in TAO with a favourable safety profile. In any case, bosentan should be further investigated in TAO patient management. To confirm initial promising findings, larger controlled randomised trials with a control group are needed. In the meantime, bosentan should be considered as a hopeful investigational agent for treating these patients.

Keywords: Thromboangiitis obliterans, endothelin, endothelial dysfunction, bosentan, nitric oxide.

## INTRODUCTION

Thromboangiitis obliterans (TAO) or Buerger´s disease is a thrombotic, occlusive, non-atherosclerotic segmental vasculitis that affects small and medium-sized arteries and veins, which may involve distal vessel of upper and lower extremities.[1] TAO usually occurs in people around the age of 45, and is more frequent in male smokers. Intermittent claudication and, in more advanced cases, pain at rest are the predominant clinical symptoms. Involvement of both the upper and lower extremities and the size and location of affected vessels help distinguish it from atherosclerosis. Distal ischaemic lesions, as ulcers, are also frequently observed. Raynaud's phenomenon is present in >40% of patients with TAO and may be asymmetrical. Skin disorders, such as migrating thrombophlebitis, may be associated with TAO, may predate the onset of ischaemic symptoms caused by arterial occlusive disease, and frequently parallel disease activity. Although most common in the extremities, TAO may also involve the cerebral, coronary, renal, mesenteric, and pulmonary arteries. Clinical course is characterised by alternating periods of exacerbation with periods of remission. Angiographic studies reveal a distal and segmental involvement of the vasculature of the extremities. Recanalisation is frequently demonstrated, showing a typical image (corkscrew collateral vessels).

Recently, novel pathways have been implicated in the physiopathology of the disease. Endothelin-1 (ET-1) has been associated in these aetiological processes by provoking endothelial dysfunction, causing complications such as vascular damage and vessel occlusion.[2,3]

Interestingly, an impaired endothelium-dependent vasodilatation in the peripheral vasculature, even in the non-diseased limbs, has been shown in patients with TAO.[4]

ET-1 is an endothelium-derived peptide, which is involved in the regulation of vascular function under normal physiological conditions by targeting two transmembrane receptors (ETA and ETB).[5] On the other hand, it plays a key role in vascular

pathologies by exerting various deleterious effects. These include hypertrophy of vascular smooth muscle cells, cellular proliferation, fibrosis, increasing of vascular permeability, activation of leukocytes, and induction of cytokine and adhesion molecule expression.[5] Moreover, ET-1 is the most potent natural vasoconstrictive mediator. In fact, it has been demonstrated that its exogenous administration in healthy volunteers produces a marked dose-dependent reduction of the blood flow[6] (Figure 1).

Elevated circulating levels of ET-1 have been repeatedly observed in TAO and scleroderma, as well as in various other pathologies of the vascular endothelium.[7-9] An increase has been detected in plasma levels of ET-1 in situations of chronic or acute coronary ischaemia, stroke, and peripheral arterial disease.[10,11]

Meanwhile, experimental studies in animal models of hypertension[12,13] and atherosclerosis[14] have shown an improvement in the endothelial function of large arteries, following short-term administration of endothelin receptor antagonists. In any case, these data indicate that some of the endothelin-mediated deleterious effects on the vasculature may be reversible.

## BUERGER'S DISEASE PATHOPHYSIOLOGY

### Effects of Bosentan

Bosentan, an oral dual ET-1 receptor antagonist, can exert a selective vasodilator effect on the diseased vascular bed in addition to its antifibrotic, anti-inflammatory and antiproliferative effects[15] (Figure 2). Otherwise, endothelial dysfunction is considered to be an early event in the onset stages of vasculitis, such as Buerger's disease, and peripheral arterial disease.[11,16] Nitric oxide (NO), in turn, is also involved in the homeostasis of endothelial function.[17] An increase in ET-1 activity has been associated to an inhibition of NO synthesis.[18]

Moreover, recent investigations have suggested that an improvement in endothelial function would be achieved by enhanced NO production.[16] Thus, the treatment with bosentan may improve NO synthesis in patients with TAO due to its inhibitory action on endothelin receptors. Accordingly, several studies have shown that bosentan can improve endothelial function after 4 weeks of treatment, indirectly demonstrated by the increasing of the flow-mediated dilation (FMD) measurements in the brachial artery in patients with systemic sclerosis, diabetes mellitus, microalbuminuria, and peripheral artery disease[11,16,19] (Figure 3).

These data allow us to hypothesise that the improvement of endothelial dysfunction, after bosentan treatment, may not only be associated with haemodynamic changes, anti-inflammatory processes, or activated-endothelium effects, but rather may be due to the enhancement of NO production following inhibition of ET-1, as has previously been seen in pulmonary hypertension.[20] These findings prove that the endothelin receptor system is an important molecular pathway that is directly involved in certain reversible aspects of vascular injury.

### Efficacy of Bosentan

Bosentan efficacy has been demonstrated, with a favourable safety profile, in two randomised controlled clinical trials, RAPIDS-1 and RAPIDS-2, for the treatment and prevention of digital ulcers in patients with systemic sclerosis.[21,22] These results suggest that it may be beneficial for the treatment of Raynaud's phenomenon. Moreover, there is increasing evidence that bosentan exerts a selective vasodilator effect and anti-inflammatory effects in patients affected by TAO,[23] comparable to such effects observed in connective tissue diseases.

To date, the only treatment that has been shown to be effective in TAO is complete abstention from smoking. Both clinical improvement and complete healing of the ulcers have been achieved in the majority of patients after quitting smoking. In spite of this, the disease progresses in up to 30% of cases, finally resulting in limb amputation.[24] Furthermore, quitting smoking is achieved in a very low number of these patients; inferior to 30% in most studies.[23] This unsatisfactory rate, in accordance with previous reports, highlights the fact that it is extremely difficult for patients who are heavy smokers to give up smoking despite having been strongly advised to do so, as well as having received full information about the benefits of quitting smoking, especially in terms of avoiding amputations.[25]

Only a few pharmacological and surgical options (of controversial efficacy) are available to encourage healing of ulcers in TAO.[26] Vasodilators, antiplatelet agents, anticoagulants, and corticosteroids appear to be of no use.[26] Prostaglandin analogues are beneficial when administered intravenously, although their efficacy is controversial on oral administration. A randomised clinical trial of intravenous iloprost

versus aspirin[27] has shown that the healing of ulcers is higher in patients who have received treatment with intravenous prostaglandins. In contradiction to this, other randomised trials have proven an oral formulation of iloprost not to be better than placebo with regard to this outcome.[28] Therefore, the efficacy results shown by prostacyclin analogues when used for the management of TAO are far from satisfactory.

Meanwhile, lumbar sympathectomy may alleviate the pain and improve superficial ulcers, but it does not prevent or reduce the ratio of amputations.[26] Surgical revascularisation is not usually feasible because of the diffuse and segmental character of the disease. Thus, new therapeutic options with a higher efficacy than the current ones are clearly needed in order to properly manage patients affected by TAO. However, the low incidence and lack of effective treatments contribute to serious difficulties in carrying out large prospective studies that confirm the efficacy of novel therapy in this particular disease, in controlled randomised clinical trials.

There are few articles published regarding the treatment of TAO with bosentan. However, they have increasingly shown that bosentan therapy is associated with several clinical and endothelial function-related outcomes in patients with TAO, which may be promising.

The anti-inflammatory, antifibrotic and selective vasodilator properties of bosentan have been shown to alleviate pain at rest and reduce the size of ischaemic ulcers caused by damage mainly to the microcirculation.[7,15,23] Recently, a single-centre clinical study has been published where 12 patients (13 extremities) previously diagnosed with TAO received treatment with bosentan in a compassionate use programme.[23] Bosentan therapy consisted of a month's treatment with 62.5 mg twice a day followed by a 125 mg BID dose after the first month. The full-dose regimen was maintained for the following 3 months or until total healing of the ulcers. Prior to the treatment with bosentan, 10 of 12 patients had previously been treated with a 21-days prostaglandin regimen, 3 had undergone revascularising procedures and 3 patients had a lumbar sympathectomy; all of those treatments with lack of success. Clinical improvement was observed in 12 extremities treated (92%), while only one extremity required major amputation below the knee. 10 extremities (77%) achieved complete clinical therapeutic success (healing or complete pain relief). A minor amputation of one toe was performed with conservation of the extremity. Also, a significant statistical improvement of the endothelial function, assessed by means of the FMD, was observed.

Several case reports have also been published in the literature. All of them provide information on TAO patients with a history of insidious necrotic ulcers with poor outcomes despite smoking cessation and conventional medical treatment, including intravenous prostaglandins.[29-31] Their results show that treatment with bosentan is able to obtain a favourable clinical and angiographic response with healing of ulcers, as well as the disappearing of the rest pain. Furthermore, most patients remained asymptomatic for 6 months after treatment cessation. Therefore, beneficial effects of bosentan in TAO patients have been reported not only during the acute phase of ulcers and rest pain, but also to extend over time.

Although these results are from a small study and case reports and are not comparable with those from randomised trials, they seem to be hopeful.

A likely explanation for the bosentan pharmacodynamic effect on endothelial function has been related on its capacity of improving endothelial function based on the endothelial function impairment observed in patients with peripheral arterial disease in general,[11] and in TAO patients in particular,[23] after treatment. Moreover, an elevated serum ET-1 level has been observed in patients with TAO, supporting a possible mechanistic explanation of the clinical benefit of bosentan in these patients.[32] Additionally, bosentan can exert a selective vasodilatory and anti-inflammatory effect on the vascular bed in patients affected by TAO, comparable to the effects observed in connective tissue diseases such as scleroderma, with the added complication of digital ulcers and peripheral arterial disease[21-23,33] (Figure 3).

## CONCLUSION

In summary, bosentan should be investigated further with regard to TAO patient management. The hypothesis that bosentan treatment in TAO patients results in an improvement of clinical, angiographic and endothelial function outcomes is supported by the results of a small pilot study and several case reports that have been recently published. However, larger prospective studies and comparative randomised trials are needed to confirm this initial evidence.

Fig. 1

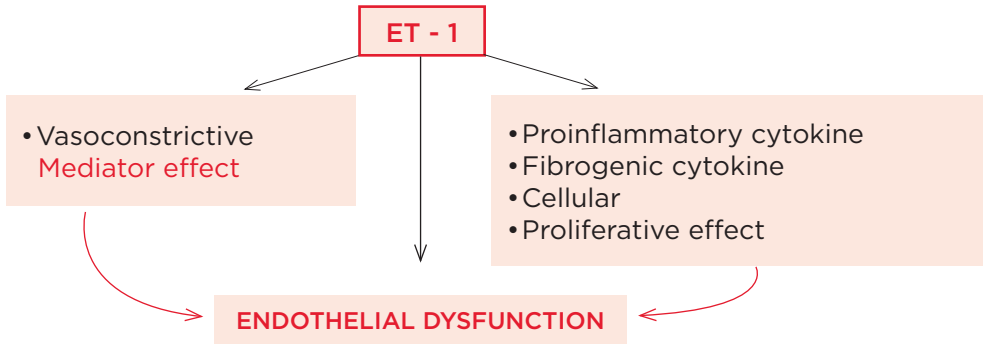


Fig. 2

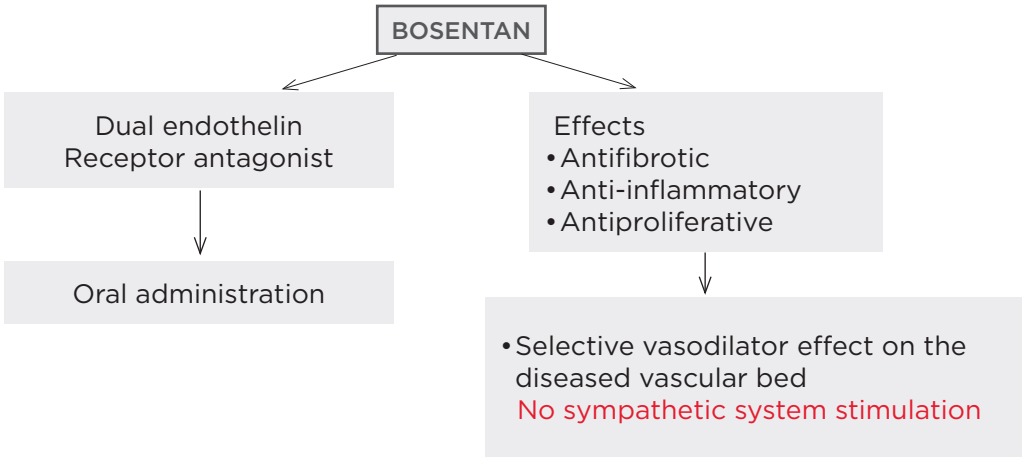


Fig. 3

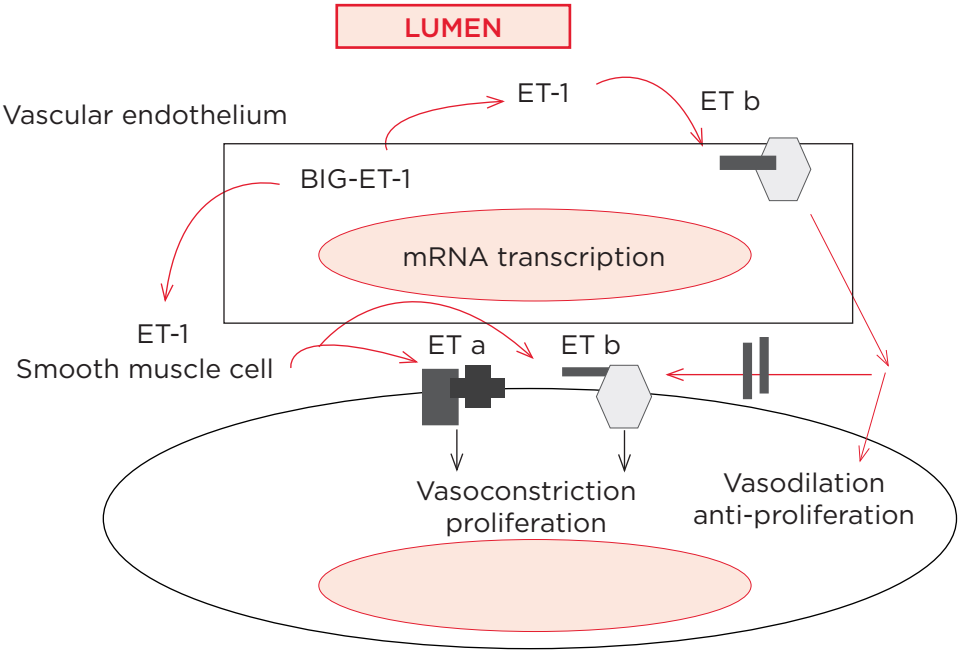


**Figure 1. Major determinants of the relationship between increased plasma concentrations of endothelin-1 (ET-1) and endothelial dysfunction.**

**Figure 2. Effects of bosentan on vascular etiopathogeny.**

**Figure 3. Biology of the endothelin system and its receptors on endothelium and smooth muscle cells.** The ET-A and ET-B are both present on smooth muscle cells, where they mediate vasoconstriction. The ET-B receptor is also present on the endothelium, where it exerts numerous effects: clearence of circulating endothelin, inhibition of endothelin synthesis, production of vasodilators, and production of vasoconstrictors. (Modified from Dupuis J. The Lancet. 2001;358:1113-4).

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