Bosentan for the treatment of scleroderma

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Bosentan is the first orally active, high-affinity endothelin dual receptor antagonist approved for the treatment of pulmonary arterial hypertension. Elevated circulating levels and increased tissue expression of endothelin-1 are characteristic of scleroderma and patients demonstrate endothelin receptor overexpression in affected tissues and organs. Two randomized trials have demonstrated that bosentan is effective in idiopathic pulmonary arterial hypertension and in pulmonary arterial hypertension related to connective tissue diseases, particularly scleroderma, improving 6-min walk distance, hemodynamic parameters and time to clinical worsening. Extension of these two pivotal randomized studies has demonstrated in the pulmonary arterial hypertension connective tissue disease subgroup (including 79% scleroderma and 12% systemic lupus) survival of 85.9 and 73.4% at years 1 and 2, respectively. The tolerability of bosentan is good in scleroderma patients. The postmarketing surveillance program (Actelion TRAX) demonstrated that elevated liver enzymes after treatment initiation were recorded in 9.4% of the 1070 scleroderma patients treated with bosentan by November 19, 2004, compared with 8.4% in idiopathic pulmonary arterial hypertension patients. For digital ulcers in scleroderma, two randomized clinical trials supported the efficacy of bosentan for the prevention of new digital ulcers (up to almost 50% less new digital ulcers). The treatment effect appeared more pronounced in the most severe cases (patients with three or more digital ulcers at baseline). However, bosentan did not demonstrate beneficial effect on scleroderma interstitial lung disease after 1 year of treatment in a randomized, controlled study. Whether a subgroup of scleroderma patients with interstitial lung disease benefit from bosentan requires further investigation. Another randomized, controlled study performed in idiopathic pulmonary fibrosis has demonstrated a treatment effect on time to disease progression or death in the subgroup with biopsy-proven idiopathic pulmonary fibrosis.

Scleroderma (SSc) is a chronic disease resulting from primarily vascular, in addition to autoimmune and proliferative, disturbances. The reported prevalence of scleroderma varies, with an occurrence of 30.8–286 cases per million. A recent evaluation of the prevalence in the Detroit area (MI, USA), based on a capture–recapture analysis, demonstrated a prevalence estimate of 276 cases per million adults [1]. Using the same methodology, Le Guern and colleagues demonstrated that the prevalence of SSc in Seine-Saint Denis (a suburb of Paris, France) was 158.3 (95% confidence interval [CI]: 129–187) per/million adults [2]. Women are more likely to be affected (3:1–6:1), with an average age at diagnosis of 40–50 years or younger. Survival at 5–6 years has been reported to be 34–76%, with an increased mortality rate of up to fourfold that of the general population [3–7]. However, more recent reports suggest that survival is higher than initially thought in unselected SSc populations [8,9]. This is probably due to an earlier diagnosis, the use of acetylcholineesterase (ACE) inhibitors in the treatment of renal crisis, a multidisciplinary approach to the disease and the diffusion of general recommendations to take care of patients.

The disease is classified based on early presentation and progression of cutaneous extension. Classification is specified as diffuse SSc (dSSc), limited cutaneous SSc (lcSSc; known as CREST syndrome) or limited scleroderma (known as SSc sine scleroderma). Boxes 1 & 2 outline the definition of these various disease states [10–12].

The understanding of the pathogenesis of SSc is still incomplete. Microvascular dysfunction, endothelial cell injury and increased collagen synthesis occur at the early stage of the disease. Treatment aims to stop the underlying disease processes and reduces fibrosis [13,14]. Digital ulcers occur in almost half of the patients and is a major cause of disability [15]. Pulmonary arterial hypertension (PAH; observed in 10–15% of cases), heart and lung involvement (observed in 10.1 and 31.7%, respectively) are currently the main causes of death in these patients [15–17].

Keywords: bosentan, digital ulcer, endothelin dual receptor antagonist, interstitial lung disease, pulmonary arterial hypertension, scleroderma

future medicine

Box 1. Preliminary clinical criteria for the classification of systemic sclerosis (scleroderma).

Major criterion (proximal scleroderma):

- Skin changes characterized by tightness
- Thickening and nonpitting induration
- Proximal to the metacarpophalangeal or metatarsophalangeal joints, affecting other parts of the extremities, face, neck or trunk (thorax or abdomen), usually bilateral and almost always including sclerodactyly

Minor criterion:

- Sclerodactyly
- Digital pitting scars of fingertips or loss of substance of the distal finger pad
- Bibasilar pulmonary fibrosis

One major or two minor criteria are required for confirmation of the presence of scleroderma.
ARA Scleroderma Criteria Cooperative Study [10].

Endothelin & the therapeutic concept of endothelin receptor blockers

Endothelin-1 was first identified in 1988 as a naturally occurring peptide with potent and long-lasting vasoconstrictor effects [18]. Several systemic rheumatic diseases, such as SSc and systemic lupus erythematosus (SLE), are characterized by elevated levels of circulating or tissue endothelin, or both [19,20]. In addition, a number of pulmonary vascular and parenchymal diseases are associated with increased levels of endothelin-1, most notably PAH [21] and idiopathic or SSc-associated pulmonary fibrosis [22,23]. Plasma levels of endothelin-1 are low in healthy individuals (1–2 pg/ml), but increase in various diseases, such as idiopathic PAH (IPAH). Endothelin-1 circulating levels correlate with hemodynamic variables, 6-min walk distance (6MWD) or survival [24,25]. A shorter life expectancy has been reported in PAH patients with elevated levels of endothelin-1 compared with PAH patients with lower levels of endothelin-1 [26]. Circulating endothelin-1 levels are also elevated in a variety of other conditions or diseases, such as PAH associated with congenital heart disease [27–29], systemic hypertension, atherosclerosis or heart failure, and the extent of the elevation correlates with the prognosis of the disease [30]. Endothelin-1 has essential developmental and regulatory roles in normal physiology, including cardiovascular homeostasis, salt and water balance, and respiratory development [31], but endothelin-1 is also a pathogenic mediator with a number of deleterious effects, including fibrosis, vascular hypertrophy and inflammation [23,32]. Endothelin-1 binds to two receptor subtypes, endothelin receptor type A (EDNRA; also termed ET_A) and endothelin receptor type B (EDNEB; also termed ET_B). ET_A receptors, which are expressed on pulmonary vascular smooth muscle cells, are potent mediators of

Box 2. Criteria for the classification of limited scleroderma.

SSc sine scleroderma:

- Raynaud's phenomenon (objectivey documentated or direct measurement of response to cold)
- Plus any one of:
  - Abnormal wide-field nailfold capillaroscopy (consisting of dilatation and/or avascular areas)
  - SSc selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, antifibrillin or anti-RNA polymerase I or III in a titer of 1:100 or higher)

Limited SSc:

- Criteria for SSc sine scleroderma plus distal cutaneous changes

Limited scleroderma was formerly known as CREST syndrome: calcinosis, Raynaud's phenomenon esophageal involvement, sclerodactyly and telangiectasia [11].

vasoconstriction and cellular proliferation [33]. ET_B receptors, which are expressed both on vascular endothelial cells and smooth-muscle cells, are primarily involved in vasodilatation and endothelin clearance, but can also mediate vasoconstriction in some pathological states. ET_A and ET_B on smooth muscle cells not only mediate vasoconstriction, but also contribute to the vascular remodelling effects of endothelin, including cellular proliferation, fibrosis and inflammation [23,31,32,34,35]. Moreover, to reverse the profibrotic effects of endothelin, antagonism of both ET_A and ET_B receptors may be necessary [36]. Bosentan is a dual endothelin receptor antagonist (ERA). Sitaxentan and ambrisentan are two selective or predominantly ET_A antagonists.

In SSc, the pathophysiological basis for the abnormal vascular response is thought to involve endothelial cell injury, pericyte activation, myofibroblast formation, vascular fibrosis and proliferation. Elevated circulating levels and increased tissue expression of endothelin-1 are characteristic of SSc [23,37], and patients demonstrate endothelin receptor overexpression in affected tissues and organs [31]. Endothelin, which is known to stimulate the synthesis of extracellular matrix as well as fibroblast and smooth muscle cell proliferation, is believed to be implicated in the formation of structural vascular lesions in SSc [18,37]. Therefore, blocking the effects of endothelin-1 using ERAs might be of particular benefit to patients with SSc. In experimental models, the dual ET_A and ET_B antagonist – bosentan – was efficacious in reducing pulmonary and cardiac fibrosis [33,38,39].

The ability of bosentan to block the deleterious effects of endothelin translates into clinical benefits in patients with PAH, resulting in significant short-term and long-term clinical improvements [40–44].

Bosentan: characteristics

Chemistry

Bosentan is chemically described as 4-tert-butyl-N[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2´]bipyrimidinyl-4-yl]-benzenesulfonamide monohydrate). Its formula is $C_{27}H_{29}N_5O_6S.H_2O$ and it has a molecular weight of 569.64 g/mol (Figure 1).

In the solid state, bosentan is very stable, it is not hygroscopic and it is not light sensitive. The marketed formulations are 62.5 and 125 mg in film-coated tablet form.

Pharmacodynamics

In a rat model of hypoxia-induced PAH, pretreatment with bosentan prevented the acute pulmonary vasoconstrictor response to hypoxia. Prolonged bosentan treatment, introduced before hypoxia exposure, prevented the development of PAH and the remodeling of small pulmonary arteries. Moreover, when bosentan was introduced 2 weeks after hypoxia exposure, it was able to improve pulmonary artery pressure and the pulmonary vascular remodeling [45].

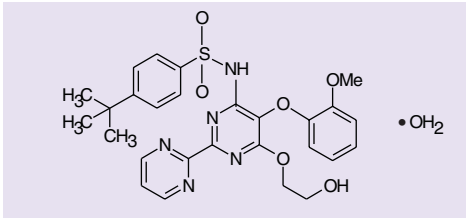
In humans, bosentan decreases pulmonary artery pressure and pulmonary vascular resistance in both congestive heart failure and PAH [46]. Bosentan has been shown to lower blood pressure in patients with essential hypertension without changes in the heart rate [47]. Moreover, the increased serum levels of metalloproteinase-9 observed in bosentan-treated patients suffering from SSc-related PAH suggests that bosentan interacts with tissue remodelling [48]. It has been shown that bosentan reverses the development of renal fibrosis in hypertensive mice models [49] and has a strong antifibrotic effect in animal models of cardiac fibrosis [50].

Pharmacokinetics & metabolism

Bosentan is rapidly absorbed and raises its maximum plasma concentration within 2 h after a single oral dose of 100 mg in healthy adults [51]. Steady state is reached within 3–5 days. The mean absolute bioavailability is approximately 50%. Steady-state levels in patients with PAH are approximately twofold higher than in healthy patients, and there is 50% variability between subjects. There is a 22% increase in peak plasma concentration when bosentan is ingested with food, although this difference is not clinically significant. No clinically significant differences in the disposition of bosentan have been observed between sexes or racial groups. Nearly 98% plasma protein binding of bosentan occurs, most of which is to albumin. The free fraction of Ro 48-5033, the primary active metabolite of bosentan, is threefold higher than bosentan. There are three metabolites of bosentan that have been identified in plasma, although a proportion of bosentan is excreted unchanged [52].

Bosentan is metabolized by cytochrome P450 (CYP)2C9 (60%) and CYP3A4 (40%). Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been studied.

Figure 1. Bosentan.



The combination should be used with caution. Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole or ritonavir) and a CYP2C9 inhibitor (e.g., voriconazole) with bosentan is not recommended.

Nearly 95% of orally administered bosentan is eliminated into feces, with the remaining expelled in urine. Hepatic metabolism and subsequent biliary excretion is the major pathway for bosentan removal, and there is no evidence for an enterohepatic circulation. The mean terminal half-life for bosentan is 3.3 h and 10–14 h for Ro 48-5033 [53].

Bosentan is also an inducer of the CYP isoenzymes CYP2C9 and CYP3A4. *In vitro* data also suggest an induction of CYP2C19. Consequently, plasma concentrations of substances metabolized by these isoenzymes will be decreased when bosentan is coadministered. Coadministration of bosentan and cyclosporine A is contraindicated because blood concentration of bosentan was approximately 30-fold higher than those measured after bosentan alone; blood concentration of cyclosporine A decreased by approximately 50%. Similarly, the concomitant use of bosentan and tacrolimus and sirolimus is not advisable because it may result in increased concentration of bosentan. The mechanism of these interactions is unknown. Bosentan should not be used concomitantly with glibenclamide, due to an increased risk of elevated liver aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). Both glibenclamide and bosentan inhibit the bile salt export pump, which could explain the elevated aminotransferases. An alternative antidiabetic medicinal product should be used in patients in whom an antidiabetic treatment is indicated. Since estrogens and progestatives are partially metabolized by CYP450, there is a possibility of failure of contraception when bosentan is coadministered. Therefore, women of childbearing potential must use an additional or an alternative reliable method of contraception when taking bosentan. Clinical experience of concomitant administration of bosentan with warfarin in patients with PAH did not result in clinically relevant changes in international normalized ratio (INR) or warfarin dose (baseline vs end of the clinical studies). No dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated but intensified monitoring of INR is recommended, especially during bosentan initiation and the uptitration period. Coadministration of bosentan (125 mg twice daily) and sildenafil (80 mg three-times daily) decrease area under curve of sildenafil by 63% and increase area under curve of bosentan by 50%. In the postmarketing surveillance program (the TRAcleer eXcellence Postmarketing Surveillance or Actelion [TRAX]), 218 patients received bosentan in combination with sildenafil and safety findings in the combination group were comparable to those in patients receiving bosentan without sildenafil. There are no known interactions between epoprostenol and bosentan during coadministration.

Concerning the use of bosentan in patients with liver disease, dosing does not need to be adjusted for patients with mild hepatic dysfunction (Child-Pugh class A), but due to the risk of liver enzyme elevation, bosentan is contraindicated in patients with Child-Pugh class B or C. Nevertheless, careful liver transaminases monitoring is recommended when bosentan is given to patients in Child-Pugh class A. Since bosentan metabolites have low pharmacological activity compared with bosentan, no dosage adjustments are needed in case of renal failure. It is expected that bosentan would be poorly removed by dialysis in view of its large molecular weight and high plasma protein binding, although this has not been studied.

Clinical evidence

Bosentan for PAH

Two randomized clinical trials led to the approval of bosentan in the USA and EU for PAH patients who are classified as New York Heart Association (NYHA)/WHO functional class III or IV (only functional class III in the EU) [40,41]. The first multicenter, randomized, placebo-controlled study of oral bosentan (study 351) was performed in 32 patients (NYHA

functional class III) with IPAH (n = 27) or PAH associated with SSc (n = 5) [40]. Patients in the bosentan-treated group received the drug at a dose of 62.5 mg twice daily for 4 weeks, and at a dose of 125 mg twice daily thereafter for a total of 12 weeks. The primary end-point was exercise capacity (6 MWD); secondary end points included hemodynamic parameters (assessed by right-heart catheterization) changes in NYHA functional class and time to clinical worsening. Clinical worsening was defined as death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation of treatment, a need for epoprostenol therapy, or atrial septostomy. The intention-to-treat analysis after 12 weeks demonstrated statistically significant improvements in the 6MWD test in the bosentan-treated group compared with placebo, with a mean treatment effect of 70 m (the distance walked in 6 min after 12 weeks of treatment lengthened from 360 m at baseline to 430 m after 12 weeks in the bosentan-treated group, whereas no change was observed in patients in the placebo group). Improvement was also observed in pulmonary vascular resistance, which is a major factor determining disease progression and prognosis in PAH: a decrease of 223 dyn × s × cm^{-5} was observed in the bosentan-treated group, whereas an increase of 191 dyn × s × cm^{-5} was observed in the placebo group. Last, patients on bosentan had a reduced Borg Dyspnoea Index (-1.6) and an improved NYHA functional class.

In the pivotal bosentan randomized trial of endothelin antagonist therapy (BREATHE)-1 study, 213 patients in NYHA functional class III or IV (of which 150 patients had IPAH, 47 PAH-SSc and 16 SLE-PAH) were randomly assigned to receive placebo or bosentan (at a dose of 62.5 mg twice daily for 4 weeks, thereafter either 125 or 250 mg twice daily for at least 12 weeks) [41]. The mean effect of treatment on the 6 MWD test was an improvement of 44 m in the combined bosentan groups placebo corrected ($p < 0.001$). Patients receiving bosentan also had a significant improvement in the time to clinical worsening. A substudy in 85 patients demonstrated that bosentan also improved right ventricular systolic function and left ventricular early filling, and lead to a decrease in right ventricular dilatation and an increase in left ventricular size in patients with PAH [42]. Analysis of survival of 169 IPAH patients from both bosentan randomized trials and their open-label extensions treated with first-line bosentan revealed a 1- and 2-year survival of 96 and 89%, respectively [43]. This rate compared very favor with a predicted survival of 69 and 57%, respectively, for these individuals based on a validated National Institute of Health (NIH) survival equation reflecting the natural history of the disease treated with conventional therapy [54]. Overall, a 5.5% annual death rate was reported for patients receiving first-line bosentan therapy in this study. Nevertheless, such a figure in survival is not applicable to PAH-SSc, which is known to have a worse prognosis than IPAH. Before the ERA era, the 2-year survival of PAH-SSc patients ranged from approximately 40 to 63% [16,55,56]. In the subgroup analysis that summarizes patients with PAH related to connective tissue diseases (n = 66; 52 SSc, 8 SLE and six others) from the two pivotal studies, the mean effect of treatment on the 6 MWD test was improved by 22.1 m (95% CI: -32; 76) at study end (week 12 or 16) compared with the 22 PAH-CTD patients on placebo, thus leading to a trend in favour of bosentan, but this did not reach statistical significance [57]. Although 95.5% of the patients were in WHO functional class III (4.5% in class IV), there were differences suggesting more severe disease in the bosentan subgroup at baseline (6MWD was 312 m vs 361; $p = 0.01$). There was a trend to slower disease progression for bosentan in term of time to clinical worsening.

There are now have three studies presenting long-term survival of PAH-SSc patients treated with bosentan (Table 1). The outcome analysis focusing on mortality of the subgroup of patients with PAH-CTD based on patients who participated in the two randomized studies and their open-label extensions is now published [57]. Of the 66 PAH related to connective tissue diseases patients, 64 continued onto the open-label studies. Of these, 40 remained on bosentan monotherapy, 1 received prostanoids in addition to bosentan, and 23 discontinuations were recorded during the follow-up period (five deaths, seven with elevation of liver enzymes, four with aggravation of PAH, two withdrawal of consent, two with hepatitis and three others). The patients were exposed to bosentan for an average of 1.6 ± 0.9 years, and the average duration of observation was 1.8 ± 0.8 years. Eight patients (16%) received epoprostenol as add-on therapy and seven patients (14%) received this drug after discontinuation of bosentan. The 6 MWD in bosentan monotherapy patients increased from 352 ± 94 m at the beginning of

Table 1. Long-term survival of pulmonary arterial hypertension-scleroderma patients treated with bosentan in large cohorts.

Parameter	Williams [58]	Denton [57]	Guillevin [59]
Centers	Single PAH-SSc center	Investigators from the two pivotal randomized studies	23 SSc centers
Methods	Consecutive PAH-SSc patients compared with historical control group (n = 47)	Subgroup analysis, randomised plus open label extension study	Single arm observational
n	45 from one expert center	66 from clinical trials	53
Mean age (years ± standard deviation)	60 ± 11.3	57.4 ± 12.6 (n = 44 bosentan group) 49.7 ± 12.7 (n = 22 placebo group)	6.3 ± 13
Type of CTD	100% SSc	79% SSc,12% SLE	80% SSc, 9% SLE or mCTD
Diagnosis of PAH	RHC	RHC	RHC
Baseline characteristics			
NYHA class	58% III; 42% i.v.	95.5 III; 4.5 i.v.	100% III
6MWD (m)	207	312 ± 12 in bosentan group 361 ± 67 in placebo group	ND
mPAP on RHC (mmHg)	40 ± 11.8	47 ± 12 in bosentan group 45.1 ± 10.6 in placebo group	39.5 ± 12.6
Observation duration	2002–2004	1.8 ± 0.8 years	48 weeks
Therapeutic effect			
Improved WHO functional class	46%‡	25%*	28%
6MWD	ND	+14.7 ± 80 m*	ND
ACW	ND	90.3% at week 16	68%
Survival	81% after 1 year 71% after 2 years	85.9% after 1 year 73.4% after 2 years	92% at week 48
Treatment	3 months after the diagnosis of PAH, ~60% of the patients were on bosentan; 12 months after the diagnosis, 45% of the patients were still on bosentan. During the observational period, 31% were transfered to prostanoid due to clinical worsening (five of them remained on bosentan); 13% stopped bosentan due to abnormal liver enzymes	16% received combined epoprostenol and bosentan; 14% received epoprostenol after discontinuation of bosentan	26% discontinued bosentan

**In bosentan monotherapy patients.*

‡After 6 months of treatment.

6MWD: 6-min walk distance; ACW: Absence of clinical worsening at the end of the study; CTD: Connective tissue disease; mCTD: Mixed CTD; mPAP: Mean pulmonary artery pressure; ND: Not determined; NYHA: New York Heart Association; PAH: Pulmonary arterial hypertension; RHC: Right heart catheterization; SLE: Systemic lupus erythematosus; SSc: Scleroderma.

the long-term extension phase by +14.7 ± 80 m (95% CI: ±11; +40) at the end of the long-term extension phase. Survival on bosentan was 85.9% after 1 year and 73.4% after 2 years.

Recently, Williams and colleagues measured survival in two groups of equally matched patients with PAH-SSc: those treated before 2002 with conventional medical therapy and prostanoids if needed (historical control group, n = 47), and those treated with bosentan as preferred treatment (current era, 45 patients) [58]. Survival rate at 1 year was 68% in the historical group, compared with 81% in the current era; the 2-year survival was 47 versus 71% in the historical control and current era groups, respectively. Since this was not a randomized, controlled study and some patients received both bosentan and a prostanoid, it is not posssible to attibute this better 2-year survival rate to any specific drug.

Results from a large prospective single-arm observational study of 53 patients with PAH related to connective tissue diseases (80% SSc, 9% SLE and 11% undifferentiated connective tissue disorder [UCTD]) suggest sustained benefits of first-line bosentan therapy [59]. At week 48, WHO functional class improved to class I (2%) or II (26%); (95% CI: 16–42%), and was unchanged in 57% (95% CI: 42–71%). The short form (SF)-36 health transition score improved in 57% of patients (95% CI: 41–71%) and was unchanged in 26% (95% CI: 14–41%; n = 46). The Scleroderma Health Assessment Questionnaire (SHAQ) disability index remained stable. Kaplan–Meier estimates were 68% (95% CI: 55–82%) of absence of clinical worsening at the end of treatment period, and 92% (95% CI: 85–100%) for survival at week 48. Four patients died during the study; one was on bosentan at time of death. Bosentan was well tolerated, with a safety profile comparable to that previously reported. After 48 weeks of treatment, bosentan is associated with improvement or stabilization of PAH symptoms and quality of life in a majority of patients.

These interesting results are corroborated by other publications with fewer patients. In a retrospective study reviewing 23 PAH-SSc patients who were treated with bosentan (but only two of the patients had a diagnosis using right heart catheterization), Joglekar and colleagues found that, after 3 months of treatment, an improvement in WHO functional class by one class could be observed in 57% of the patients [60]. However, after 9 months, WHO class tended to worsen compared with baseline. Three patients had to discontinue bosentan (two owing to an increase in transaminase levels and one due to fluid retention). Using bosentan as a first-line single agent for PAH in 17 scleroderma patients, with a mean time from initiation of bosentan to data analysis of 21, 3 ± 10 months (range: 6–44), Girgis and colleagues found an overall survival at 2 years of 79% [61]. In this study, 47% of bosentan patients discontinued the treatment owing to adverse events, they received an additional treatment for PAH or because they were switched to other therapies for PAH.

The increased risk of mortality and the higher severity observed in PAH-SSc compared with IPAH may be explained by several factors. Cardiac involvement in SSc is common. Myocardial microangiopathy and fibrosis lead to an impairment of systolic and diastolic ventricular function and myocardial ischemia [62,63]. The worst prognosis observed is also sometimes due to the presence of a pulmonary veno-occlusive disease associated to PAH [64], which is a relative contraindication to vasodilator therapy including epoprostenol [65]. In case of first-line bosentan monotherapy in PAH-SSc (in addition to the conventional treatment), patients must be closely monitored during the first four months of treatment. According to recent evidence-based guidelines, if clearly unsatisfactory results have been obtained on bosentan monotherapy, such as NYHA functional worsening, poor exercise capacity, deterioration in exercise capacity or low cardiac index, combination therapy might be considered for patients who fail to improve or deteriorate with first line treatment [66,67].

Combination therapy is probably one of the future therapeutic options in the more severe patients. Adding bosentan to intravenous epoprostenol was evaluated in a randomized, double-blind, placebo controlled trial of 33 patients (27 IPAH, five PAH-SSc and one lupus-PAH). All patients were severe with a functional class III or IV [68]. After 2 days of intravenous epoprostenol, patients were randomized to receive bosentan or placebo for 16 weeks. A trend for a greater improvement in hemodynamic parameters in favor of the combined therapy was observed in the patients who completed the trial (change in total pulmonary resistance: -36.3 ± 4.3% in the bosentan/epoprostenol group vs -22.6 ± 6.2% in the placebo/epoprostenol group; p = 0.08). No additional benefit in 6MWD was observed between groups with a median increase of 68 m in the epoprostenol/bosentan group compared with 74 m in the epoprostenol/placebo group (p = not specified). Statistical power was the major limitation of this study, which enrolled only 33 patients.

Adding inhaled iloprost (5 µg or placebo six-times daily up to 9 mg/day) to stable-dose bosentan patients has demonstrated its efficacy in a 12-week randomized study in 67 PAH patients [69]. The treatment effect on the 6MWD was of 26 m (p = 0.051) and time to clinical worsening was delayed in the iloprost group (p = 0.02). Inhaled iloprost may be a useful adjunct therapy in some selected PAH patients who deteriorate due to disease progression on bosentan monotherapy, but there are currently no data in PAH-SSc. The combination of bosentan and sildenafil has been tested in rat models with chronic PAH [70]. Both drugs are efficient and their combination demonstrated an additional effect for decreasing pulmonary

arterial pressure and reducing mortality. In patients with IPAH who had transient improvement with first line bosentan, adjunction of sildenafil may be safe and effective [71], but randomized trials are needed to provide evidence of the usefulness of this combination. The evaluation of potential additive effects of bosentan and sildenafil in humans with PAH is currently ongoing in different trials.

Thus, currently available data support the usefulness of the ERA bosentan in stabilizing or improving exercise capacity in patients with PAH-SSc. Long-term treatment with bosentan in PAH-SSc patients is associated with improvement or stabilization of PAH symptoms, quality of life and clinical outcome in a majority of patients.

Bosentan for digital ulcers

Medical history of digital ulcers or active digital ulcers concerns almost half of SSc patients. Ischemia due to microangiopathy, calcinosis and local skin trauma all contribute to ulcer initiation. Some patients have new digital ulcers every year (particularly during winter). Digital ulcers are frequently multiple. On average, patients present with at least two and more than half have at least four ulcers [72]. This causes disability, impairment of hand functions and difficulties in performing normal daily activities, and is frequently painful. Moreover, digital ulcers are a predisposing factor to skin infection and osteomyelitis. Healing and prevention of digital ulcer is a challenge in SSc.

Two randomized clinical trials supported the efficacy of bosentan in the prevention of new digital ulcers in SSc. The first randomized, placebo-controlled, double-blind study of 122 patients conducted in a 16-week period demonstrated a significant reduction of new ulcers during the treatment period (1.4 vs 2.7 new ulcers, $p = 0.0083$) [72]. The treatment effects were greater in diffuse-SSc and in patients with at least four active digital ulcers at study entry (the more severe cases). In both groups, approximately 50% of patients demonstrated partial to complete ulcer healing within 8 weeks. Bosentan treatment was associated with improvement in hand functions.

The second randomized, placebo-controlled, double-blind study included 188 patients during a 24-week period [73]. The total number of new ulcers per patients up to 24 weeks was 1.9 ± 0.2 with bosentan versus 2.7 ± 0.3 with placebo ($p = 0.035$). However, the effect of bosentan was blunted in subjects who actively continued to smoke (not in former smokers). The treatment effect was more pronounced in the most severe cases. Patients on bosentan with more than three ulcers at baseline developed 48% fewer new digital ulcers compared with placebo (2.3 vs 4.4, respectively). The effect on healing was not different between the two groups. SHAQ visual analog scales were significantly improved in the bosentan group at 24 weeks, with an improvement of hand functions (eating and dressing).

Several case reports and one case series suggest that bosentan may sometimes provide a dramatic improvement for active digital ulcers in some SSc patients. In the nine cases presented by Launay and colleagues, ulcer healings were observed within 2–8 weeks after the initiation of bosentan [74]. Patients mostly had severe, multiple ulcers and in two out of three of cases a diffuse form of SSc. All patients were non responders to conventional treatment, including intravenous iloprost in four cases. In conclusion, bosentan reduces the number of new digital ulcers in patients with SSc, particularly in severe cases and diffuse form of SSc. However, the effect on healing of digital ulcers has not been proven by the two randomized studies.

Bosentan for other manifestations

Lung fibrosis

Several *in vitro*, animal and human studies suggest the implication of ET-1 in lung fibrosis. Transgenic mice overexpressing the *ET-1* gene develop pulmonary fibrosis [39]; and increased ET-1 levels have been reported in patients with pulmonary fibrosis associated with scleroderma in the absence of PAH [23]. Furthermore, bosentan was found to significantly reduce bleomycin-induced pulmonary fibrosis in an animal model [75].

There are two clinical trials of bosentan in patients with idiopathic interstitial lung disease (ILD) and ILD associated with SSc that have been completed.

The bosentan in ILD (BUILD-2) study enrolled in a double-blind randomized, placebo-controlled study, 163 patients with ILD associated with SSc [73]. All patients had significant ILD on high-resolution CT (HRCT) scan, a diffusing capacity of the lung for carbon monoxide (DLCO) of less than 80% of predicted, a 6 MWD between 150 and 500 m (or >500 m with marked exercise desaturation/and a history of SSc of < 3 years or >3 years with signs of worsening of the ILD or alveolitis on bronchoalveolar lavage). There were no statistically

significant differences in primary outcome (6 MWD) or key secondary outcomes (forced vital capacity, DLCO and categorical changes in pulmonary function test [PFTs]) between bosentan and placebo-treated patients. One or both of the following factors may have affected the result (but it is difficult to judge a study that has only been presented in an abstract form):

- Use of 6MWD may not be appropriate to assess treatment effects in parenchymal lung disease;
- This study failed to select a population with expected level of disease progression, as shown by the stability of PFTs in both groups;
- ILD trials related to SSc may require a longer period of observation.

Bosentan is well tolerated in subjects with ILD associated with SSc. Nevertheless, despite these negative results in SSc, it is possible that a subgroup of patient may benefit from bosentan treatment. Indeed, in the BUILD-1 study conducted over 12 months in idiopathic pulmonary fibrosis, bosentan demonstrated a trend to delay the time of disease progression or death. In the subpopulation with biopsy-proven ILD (n = 49 in the bosentan group and n = 50 in the placebo group), treatment effect on time to disease progression or death was more pronounced and reached statistical significance (event-free patients = greater than 85% in the bosentan group compared with ~70% in the placebo group, p = 0.009). Whether a subgroup of SSc patients with ILD benefit from bosentan needs further investigations.

Myocardial perfusion

Primary myocardial involvement due to microcirculation impairment is common in SSc. Allanore and colleagues have prospectively evaluated 18 SSc patients without clinical heart failure and with normal pulmonary arterial pressure (13 women, mean age 54 ± 10 years; mean disease duration 7 ± 6 years, ten with diffuse and eight with limited cutaneous forms) [76]. After a 72-h vasodilator washout period and after four weeks of bosentan treatment (62.5 mg twice daily for 2 weeks titrated to 125 mg twice for 2 weeks) the authors observed a significant increase in MRI perfusion index (0.214 ± 0.05 vs 0.164 ± 0.05 at baseline; p = 0.006) and in systolic and diastolic strain rates (3.02 ± 0.65 vs 2.17 ± 0.42 s^{-1} at baseline, p = 0.0005, and 3.77 ± 1.47 vs 2.85 ± 1.36 at baseline; p = 0.0084, respectively). In SSc, a short-term treatment with bosentan simultaneously improves myocardial perfusion and function, as evaluated by highly sensitive and quantitative methods, suggesting a beneficial effect on vascular dysfunction; however, it is difficult to evaluate the real benefit of treatment as the patients were clinically asymptomatic before start of the therapy. Whether additional remodelling effects may be observed with long-term treatment with bosentan remains to be determined.

Safety & tolerability

Bosentan should be initiated at a dose of 62.5 mg twice daily for 4 weeks, and then increased to the maintenance dose of 125 mg twice daily. Liver enzymes must be measured prior to initiation of treatment and subsequently at monthly intervals. In addition, liver enzymes must be measured 2 weeks after any dose increase.

In the BREATHE-1 study, the number and nature of adverse events was similar in the bosentan and placebo groups, with the exception of increased levels of hepatic aminotransferases, which occurred more frequently in the bosentan groups than the placebo groups (9 vs 3%) [41]. However, none of these elevations were judged as serious by the investigators. The frequency of increased levels of hepatic aminotransferases after bosentan intake was dose-dependent.

A large body of evidence on the safety profile of bosentan in the treatment of PAH-SSc has been gathered in an extensive postmarketing surveillance program (TRAX), which was set up in May 2002 as required by the European Agency for the Evaluation of Medicinal Products [77,78]. It was established to monitor the safety of bosentan under clinical practice conditions, with particular focus on liver function, and to confirm treatment and drug monitoring algorithms. Information entered by the prescribers was directly transferred via a secure internet connection to the central database, and reviewed regularly by the manufacturer's global safety department to determine safety signals. Safety signals including adverse events, specific categories of signals including elevations of hepatic aminotransferases, other abnormal laboratory values, death and hospitalization were highlighted. As an accurate number of signals (numerators) and an accurate number of exposed individuals (denominator) were known, the true rate of signal frequency could be calculated. By November 2004, 4994 patients were included in

the database, with 28% of the total bosentan-exposed population having PAH related to connective tissue disorders (1421 patients, including 1070 patients with PAH-SSc, 130 with mixed connective tissue disease and 107 patients with SLE-associated PAH). When focusing on patients with PAH-SSc, 2.7% were in NYHA class I, 13.0% in class II, 64.3% in class III, and 12.2% in class IV (classification missing for 7.9%). Concomitant medications at baseline included prostanoids in 17.5% and anticoagulants in 42.9%. Mean exposure to bosentan was 38.1 (±31.1) weeks. A total of 328 patients (32.3%) were treated with bosentan for at least 1 year. At least one safety signal was recorded in 34.4% of PAH-SSc patients, which was comparable to those observed in IPAH patients (36.7%). Elevated ALT and/or AST values after bosentan initiation were recorded in 9.4% of patients with PAH-SSc and 8.4% of IPAH patients. The median time to onset of ALT or AST elevations was 71 days. No cases of fatal or permanent liver injury were associated with bosentan. The TRAX data confirm that bosentan was well tolerated, with a frequency and severity of liver function test abnormalities consistent with those observed in controlled clinical trials [77,78]. When bosentan is given to SSc patients in case of digital ulcers, there is no difference in safety profile when compared with PAH patients. In five of 79 patients in the bosentan group from the first randomized study, liver abnormalities definitively stopped the drug [72]. In the second randomized study, ten patients in the bosentan group (10.5%) had a level of transaminases greater than three-times the upper limit [79]. All liver enzymes elevations were reversible upon treatment discontinuation. The analysis provides supportive evidence for long-term safety of bosentan in patients with PAH-SSc in daily medical practice, and reinforces the necessity to monitor hepatic aminotransferases monthly. Elevations in liver aminotransferases have been also described with other ERAs, including ET_A-selective antagonists (sitaxsentan, ambrisentan), thereby emphasizing the fact that these side effects are a class effect of ERAs. Elevation of liver enzymes might be less frequent with sitaxsentan and ambrisentan [80–82], but the current experience comprises of smaller populations and short-term evaluation. As demonstrated with bosentan, elevations in liver aminotransferases are dose-dependent, with ET_A-selective antagonists highlighting the importance of achieving a better risk–benefit ratio in order to have a better safety profile.

Furthermore, it is recommended that hemoglobin concentrations are checked prior to initiation of bosentan, and after every month during

Executive summary

Mechanism of action

- Bosentan is an endothelin (ET) dual-receptor antagonist that blocks both ET type A (ET_A) and ET_B receptors.
- Antagonism of ET_A and ET_B receptors inhibits ET-induced vasoconstriction and vascular remodelling.

Pharmacokinetic properties

- Bosentan blocks ET_A and ET_B receptors with high affinity.
- Bosentan has a drug elimination half-life conducive to twice-daily dosing.

Clinical efficacy

- Bosentan leads to an improvement in exercise capacity (6-min walk distance), time to clinical worsening and hemodynamic parameters in patients with idiopathic pulmonary arterial hypertension (PAH) and PAH related to scleroderma.
- Bosentan prevents the development of new digital ulcers in patients with scleroderma and improves hand function.

Safety & tolerability

- Less than 10% incidence of elevated liver aminotransferases in scleroderma is recorded.

Drug interaction

- Bosentan is metabolized by the cytochrome P450 (CYP) system: 60% by CYP2C9 and 40% by CYP3A4.
- Association of bosentan with other CYP3A4 and CYP2C9 inhibitors is not recommended since there is a possibility of failure of hormonal contraceptives. An additional or alternative reliable method is recommended.

Dosage & administration

- Bosentan should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Tablets are to be taken orally morning and evening, with or without food.

the first 4 months then quaterly thereafter. A decrease in hemoglobin (15% or more with a level <11 g/dl) occurred in 6% of bosentan treated patients. Diarrhea was most frequently noticed with bosentan in SSc patients in the RAPIDS-1 study (9 vs 2% in the placebo group) [72]. No significant difference was observed with bosentan compared with placebo concerning headaches and lower limb edema. Nevertheless, lower limb edema may occur in bosentan-treated subjects.

Conclusion

Despite major advances, no curative treatments for most severe scleroderma complications are currently available (including PAH, digital ulcers, cardiac involvement or lung fibrosis). However, in less than 20 years PAH patients have gone from a state of no hope to one where prolonged survival and improvements in quality of life can be achieved. Advances in medical treatments over the past decade reflect a better understanding of the underlying pathophysiologic mechanisms of scleroderma. Among those, recognition of the pathogenic role of endothelin has led to development of ERA, which are now recognized as key players in the disease and its consequences. Many unanswered questions remain to be elucidated, including the long-term efficacy of these agents in PAH complicating SSc, as well as in patients with other complications of SSc.

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