Clinical experience with bosentan and sitaxentan in connective tissue disease-associated pulmonary arterial hypertension

Christopher J. Valerio¹, Clive E. Handler¹, Peter Kabunga¹, Colette J. Smith², Christopher P. Denton³ and John G. Coghlan¹

Abstract

Objectives. To report outcomes in patients with CTD-pulmonary arterial hypertension (CTD-PAH) in an observational cohort treated with bosentan or sitaxentan and determine whether differences would justify a randomized, controlled multicentre study in this subpopulation.

Methods. Patients with CTD-PAH, diagnosed by right-heart catheter studies, were assigned to either bosentan or sitaxentan based on physician choice. All patients were followed up with repeat assessments and data were collected for the local registry database.

Results. The bosentan- (n = 32) and sitaxentan- (n = 22) treated groups had comparable haemodynamic and prognostic measures at baseline. Repeat haemodynamic assessments showed reductions in pulmonary vascular resistance with bosentan (−99 dynes/s/cm⁵, P < 0.01) and sitaxentan (−92 dynes/s/cm⁵, P < 0.05). The 6-min walk distance improved at 3 months with sitaxentan (25 m, P < 0.05). N-terminal pro-B-type natriuretic peptide levels fell in the bosentan cohort at 6 months (−70 pmol/l, P < 0.05) and 1 year (−83 pmol/l, P < 0.01). Haemoglobin fell with both drugs (at 3 months −0.5 g/dl bosentan, P < 0.05 and −0.9 g/dl sitaxentan, P < 0.005). Calculations of the difference in treatment effect did not demonstrate superiority of either therapy. The 1-year estimated clinical worsening event rates were high: 41% sitaxentan, 62% bosentan (P = 0.142), with serious event rates of 27 and 14% (P = 0.263, log-rank test), respectively. Six patients discontinued bosentan because of transaminase elevation within the first year. Estimated 1-year survival was similar in both groups and 96% overall.

Conclusion. Both sitaxentan and bosentan appear effective in CTD-PAH, but the apparent additional benefit of sitaxentan reported from the open-label Sitaxentan To Relieve ImpaireD Exercise-2X study was not confirmed in this observational cohort. Although survival has improved, event rates continue to be substantial and CTD-PAH remains a therapeutic challenge.

Key words: Pulmonary hypertension, Pulmonary circulation, Endothelin receptors, Endothelin-1, Bosentan, Sitaxentan, Systemic sclerosis, Connective tissue disease, Drugs.

Introduction

Pulmonary arterial hypertension (PAH) is an important and potentially fatal complication of CTD, notably SSc (scleroderma) [1]. Diagnosis depends upon right-heart catheterization, and despite efforts to screen patients with CTD, PAH is frequently diagnosed late due to the limitations of non-invasive screening tools. Prognosis is generally worse in CTD-PAH than other forms of PAH. The published UK registry data report a 22% 1-year mortality rate in CTD-PAH from the time of diagnosis [2].

The availability of licensed oral therapies for PAH has been a major medical advance. The first PAH-specific oral therapy was bosentan, a non-selective endothelin receptor antagonist (ETRA). ET-1 is a potent endogenous vasoconstrictor and mitogen that has been implicated in the
pathogenesis of both PAH and SSc [3]. Previous work has suggested improved survival in CTD-PAH following routine use of bosentan in eligible cases, and ETARAs are the recommended therapy for CTD-PAH [4]. The licensed ETARAs available in the UK differ in their endothelin receptor selectivity. Bosentan is a dual ETAR; it blocks Type A (ER\(_A\)) and Type B ET-1 receptors (ER\(_B\)) [5]. Sitaxentan is specific for ER\(_A\); this offers some theoretical advantages in PAH since ER\(_B\) may increase nitric oxide release from endothelial cells and also facilitate clearance of ET-1 from the circulation [6]. Both drugs have been shown in randomized, placebo-controlled trials to improve exercise tolerance and haemodynamic measures in PAH [7–9].

Unfortunately, in one of the pivotal studies that supported efficacy of sitaxentan in PAH, Sitaxentan To Relieve Impaired Exercise (STRIDE)-2, an open-label bosentan arm was included as an observational comparator for sitaxentan therapy. This study was not powered to show a statistically significant difference between the two drugs [10]. In keeping with the previous studies in PAH, a short double-blind phase was followed by an open-label extension study, STRIDE-2X. Post hoc analysis of the CTD-PAH subgroup in STRIDE-2X suggested that sitaxentan may be superior to bosentan with respect to: discontinuation of monotherapy; time to clinical worsening; and mortality [11, 12]. Subsequently, several papers have discussed the theoretical benefit of selective ER\(_A\) antagonism and the limited evidence from STRIDE-2X [13–17].

At present the STRIDE-2X data remain as the only published comparison of these two therapies. Our unit is a major centre for management of CTD-PAH and, in the absence of a prospective randomized comparison of these two drugs, we have been able to compare outcomes in an observational cohort of CTD-PAH patients treated with either bosentan or sitaxentan. This offers the opportunity for additional open-label comparison of these drugs and represents an important translation of previous trials into clinical practice.

Materials and methods

Patients

Enrolment took place during the period from November 2006 to January 2009. Patients with confirmed CTD including: dcSSc or lcSSc, SLE, SS and overlap CTD/MCTD were included. PAH was diagnosed with right-heart catheter studies showing a mean pulmonary artery pressure of ≥25 mmHg at rest with a pulmonary capillary wedge pressure of ≤15 mmHg [18].

Patients with PAH are generally treated with basic or supportive medication, including anti-coagulants (warfarin), digoxin, calcium channel blockers and diuretics. Patients taking a stable dose of sildenafil for ≥3 months before starting an ETRA were included. Patients in modified World Health Organization (WHO) functional class (FC) IV were excluded as, according to protocol, parental prostanoid is indicated as first-line therapy. No limits were placed on patient’s 6-min walk distance (6MWD) for study entry. Patients who had been treated previously with bosentan, but developed intolerable side effects or elevated transaminases (to three times the upper limit of normal) were considered eligible. A requirement was made that bosentan had been stopped for ≥3 months before sitaxentan therapy was commenced. Patients with significant pulmonary fibrosis, defined as forced vital capacity (FVC) <60% or obstructive lung disease (forced expiratory volume in 1 second: FVC ratio <60%) were excluded.

Patients consented to haemodynamic studies in writing, and verbally for other assessments and therapy. Specific consent for the study was not required as no additional assessments were performed beyond those clinically necessary. Local clinical governance officers have approved the maintenance of the Royal Free Hospital pulmonary hypertension database, and our patients are informed that their data are used to help improve patient care.

Study design and measurements

This was a real-life, unblinded, observational study of two ETARAs in patients with CTD-PAH. Except where a patient had previously received one ETRA, drug selection was made by one senior, experienced clinician (J.G.C.). Measurements recorded were: haemodynamic variables, 6MWD, N-terminal pro-B-type natriuretic peptide (NT-proBNP), WHO FC, Borg Dyspnoea Index and time to clinical worsening. In patients established on ETRA therapy, repeat haemodynamic assessment by right-heart catheterization was performed at 3 months. Serious clinical worsening events were pre-defined as: death, transplantation, atrial septostomy, hospitalization for PAH, change to parenteral PAH therapy as required clinically (usually s.c. or i.v. prostanoid) or deterioration in FC with reduction in 6MWD of ≥15% [12]. We also reviewed the records retrospectively to obtain information concerning prescription of sildenafil, oxygen, digoxin and calcium channel blockers to allow determination of clinical worsening as defined in Benza et al. [11], which includes initiation of new chronic PAH therapies. Liver transaminase and haemoglobin monitoring is mandatory for patients on ETRA therapy and the safety data were also recorded.

Data analysis

For repeated values, baseline, 3-month, 6-month and 1-year values were analysed. Intention to treat analysis was used for: 6MWD, FC, survival and time to clinical worsening. Deceased patients were assigned to FC IV and a 6MWD value of 0 m. Where data items were missing, the last observation was carried forward. Haemodynamic variables were not analysed in this manner, because repeat right-heart catheterization was not undertaken if patients were intolerant of the ETRA within 3 months of starting treatment. Monitoring blood tests for safety measures were only taken from patients on ETRA therapy.

Comparison of baseline characteristics was performed using chi-squared test for categorical values and Student’s t-test for continuous data. Parametric values for each treatment group were compared using a
two-sample Student’s t-test. Non-parametric data were analysed using the Wilcoxon rank-sum test. Comparison of clinical event rates and mortality between groups used Kaplan–Meier analysis with log-rank testing for significance. Comparison of treatment effect for parametric values was made by calculation of the net difference in change with CIs. A $P < 0.05$ was considered to be statistically significant.

**Results**

**Study population and follow-up**

After exclusion of patients with significant lung disease, there were 32 patients in the bosentan group and 22 patients in the sitaxentan group (including 6 who had previously taken bosentan). There were no significant differences between the groups (Table 1), although the power was quite low to detect differences. More patients in the sitaxentan group were taking sildenafil at the start of the study. Two patients in each group were unable to complete 6-min walk tests.

All alive patients had assessments at 6 months with no patients lost to follow-up. At point of analysis, median duration of follow-up was 709 (range 245–1182) days in the bosentan group and 586 (range 87–1170) days in the sitaxentan group. Two patients on sitaxentan did not have repeat haemodynamic assessment, one died at 87 days and the other stopped therapy. Three patients of the bosentan cohort did not have follow-up haemodynamic studies. One patient developed elevated transaminases within 2 months of starting therapy, one was commenced on parenteral prostanoids and one was hospitalized with scleroderma-related problems.

**Clinical efficacy**

There was no difference in the size of effect of the two agents on any repeated measures (Table 2). Considering the cohort as a whole, there was a significant increase in 6MWD of 17 m at 3 months compared with baseline ($P < 0.01$). Borg dyspnoea scores did not improve with either therapy. There was no significant change in FC: after 1 year there were an additional four patients in FC II (three on bosentan, one on sitaxentan) with one patient on bosentan improving from FC II to I. Seven patients progressed to FC IV (five on bosentan and two on sitaxentan) within 1 year.

**Survival and clinical worsening**

Up to the date of censor there were 10 deaths; with an overall estimated survival of 96% at 1 year. Deaths occurred at Days 300, 389, 445, 568 and 666 in the bosentan group and at Days 87, 393, 481, 693 and 788 in the sitaxentan cohort. The clinical worsening event rates were 62% (95% CI 78, 46%) and 41% (95% CI 61, 21%), respectively, in the bosentan and sitaxentan groups ($P = 0.142$, log-rank test; Fig. 1). The breakdown of events for the bosentan arm was: six alternative ETRA therapy, eight phosphodiesterase-5 inhibitor started, two digoxin, one oxygen, one parenteral treprostinil, one hospitalization and one death. In the sitaxentan group, the events were: seven addition of phosphodiesterase-5 inhibitors, one alternative ETRA

<table>
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<th>TABLE 1 Baseline characteristics of our study cohort with available STRIDE-2X data</th>
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<tr>
<td>Characteristic</td>
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<td>Bosentan</td>
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<td>n = 32</td>
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<td>6MWD*, m</td>
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Data presented as mean (s.d.) where appropriate. *Incomplete data. TLC: total lung capacity; DLCO*: carbon monoxide diffusion capacity; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure.
therapy and one commenced on i.v. treprostinil therapy. At 1 year, there were six serious worsening events (one death, two started parenteral therapy, two progressed to FC IV and one hospitalized with PAH) in the bosentan group giving an estimated event-free survival of 73% (95% CI 57, 89%). Survival free of serious events was estimated at 86% (lower 95% CI 72%) for the sitaxentan group at 1 year (4% overall) in this study, which compares favourably with registry data [2]. This may reflect several factors including: careful population selection; close monitoring; increasing use of oral combination therapies; and exclusion of patients in FC IV or with significant lung disease. Clinical worsening (Fig. 1) and mortality rates were similar with both therapies. Although the improvement in 6MWD observed with sitaxentan was almost double the effect observed with sitaxentan was almost double the effect seen in the bosentan group (25 m compared with 13 m, respectively), this was not significant. Bosentan produced an unexpected fall in mixed venous oxygen saturation; this may reflect progression of coexistent lung disease, since the arterial oxygen levels fell by a similar degree in several cases. Although NT-proBNP levels remained low in the bosentan cohort up to 1 year, only a trend was seen with sitaxentan therapy. The progressive nature of CTD-PAH may explain the apparent peak of treatment effect before 6 months, despite many patients starting additional therapy.

Tolerability and adverse events

The estimated proportion of patients continuing on initial therapy (whether in combination or as monotherapy) at 1 year was 0.63 (95% CI 0.46, 0.80) in the bosentan cohort and 0.73 (95% CI 0.55, 0.91) in the sitaxentan cohort (P = 0.608). Of the seven patients who stopped sitaxentan therapy, one died, one required parenteral therapy and one was non-compliant. The remaining four were changed to other oral therapies: two because of diarrhea and abdominal pain; one because of transaminase elevation at 259 days; and one because of other side effects. Seventeen patients discontinued bosentan: three due to death; three were converted to parenteral therapy; seven due to elevated transaminases; and four were changed to other oral therapies (two each to sildenafil and sitaxentan).

Elevated transaminase levels occurred in the first year of therapy in five bosentan patients (P = 0.262 by log-rank test, compared with sitaxentan; Fig. 1), with a further two patients developing transaminase elevation beyond 500 days. Transaminase levels returned to normal levels in all cases. Mean haemoglobin levels fell with bosentan and sitaxentan (Table 2). One patient in the bosentan group required a blood transfusion for symptomatic anaemia. One-way analysis of variance shows that the fall in haemoglobin continues to be significant in the bosentan group (n = 19, P < 0.05).

### Discussion

These data show that, consistent with randomized controlled trials, ETRA therapy improves haemodynamics in CTD-PAH [7, 9]. We observed a low mortality rate at 1 year (4% overall) in this study, which compares favourably with registry data [2]. This may reflect several factors including: careful population selection; close monitoring; increasing use of oral combination therapies; and exclusion of patients in FC IV or with significant lung disease. Clinical worsening (Fig. 1) and mortality rates were similar with both therapies. Although the improvement in 6MWD observed with sitaxentan was almost double the effect seen in the bosentan group (25 m compared with 13 m, respectively), this was not significant. Bosentan produced an unexpected fall in mixed venous oxygen saturation; this may reflect progression of coexistent lung disease, since the arterial oxygen levels fell by a similar degree in several cases. Although NT-proBNP levels remained low in the bosentan cohort up to 1 year, only a trend was seen with sitaxentan therapy. The progressive nature of CTD-PAH may explain the apparent peak of treatment effect before 6 months, despite many patients starting additional therapy.

### Comparison with trials

Previous clinical trials have included patients with CTD-PAH as a significant minority of the study population.
In bosentan randomized trial of endothelin antagonist therapy, 33 patients with SSC were treated with bosentan and 14 with a placebo. The resulting difference in 6MWD of 43 m was mostly due to decline (40 m) with placebo [7]. Analysis including patients with other CTDs and data from Channick et al. 2001 [7] (bosentan, n = 44; placebo, n = 22) reported a treatment effect of 22 m [19]. Combining CTD-PAH patient data (n = 39) from the STRIDE trials, the placebo subtracted treatment effect was 38 m with sitaxentan 100 mg [20]. Open-label extension trials have been utilized to determine mortality outcomes, e.g. combined analysis of bosentan-treated CTD-PAH patients estimated 1-year survival at 86% [19].

Figure 1 shows our clinical outcome data. Compared with the STRIDE-2X data set, our cohort has more FC III patients, more scleroderma patients, reduced average 6MWD, higher cardiac index, lower pulmonary vascular resistance and a higher rate of sildenafil use. The CTD-PAH subgroup from STRIDE-2X had a 1-year survival of 96% on sitaxentan 100 mg (n = 27) and 80% on bosentan (n = 25) therapy [11, 12]. This compares with 96 and 95% for bosentan and sitaxentan, respectively, in our cohort. The STRIDE-2X data for the CTD-PAH subgroup are unclear with a significantly better time to clinical worsening reported [12]. There is no significance level quoted for the reported clinical worsening event rates of 27% (sitaxentan) and 56% (bosentan), which includes the addition of oxygen, digoxin, calcium channel blockers and sildenafil [11]. Adopting either of the definitions of clinical worsening events used, we were not able to replicate the difference in outcomes between bosentan and sitaxentan therapy: 1 year rates were 27% (bosentan) and 14% (sitaxentan) for serious clinical events and 62% (bosentan) and 41% (sitaxentan) for clinical worsening events including any new PAH therapy. Of course, this second definition is likely to favour the sitaxentan group, as many were already on sildenafil.
ET-1 receptor selectivity

Our data do not wholly support the idea that selective antagonists of ERα produce a better clinical response than non-selective ETRAs. Experiments showing a differential response to selective blockade have been conducted in subjects with normal physiology; in PAH, the distal pulmonary vessels have more ET-1 binding sites [21]. We have not demonstrated any significant differences between a selective and non-selective ETRA strategy in our patients with PAH (Fig. 1, Table 2). Experiments have also shown that ERα and ERβ receptors can couple to form heterodimers, which may adopt the function of either. It has been hypothesized that this would allow cross-talk, whereby selective blockade is compensated for by the other receptor [14]. As the mechanism of selective ERα blockade superiority is questionable, clinical studies should be the best way to move the debate forward. The data we present with a greater increase in 6MWD with sitaxentan at 3 months but falling to equivalent levels by 6 months may reflect compensatory mechanisms.

The implication of our results for further investigation into this clinical conundrum is clear. No institution has yet come forward to conduct a prospective, randomized trial to confirm the findings of STRIDE-2X. The cost of conducting such a study would be considerable and the financial implications make for a poor business case. In the absence of this proposed trial, we can perhaps fall back on available information. Our observational study uses prospective registry data and includes similar patient numbers to the STRIDE-2X analysis. Had we shown that ERα selectivity was advantageous, the call for a randomized trial would have been strengthened. However, taking our findings into account patient numbers would need to exceed the largest trials in CTD-PAH to date. Additionally, at this stage in PAH therapy more interest is focused on combining therapies. Many trials will allow for one specific PAH therapy, e.g. sildenafil, but this may make data more difficult to interpret as we have found.

Adverse events

The incidence of liver transaminase elevation tended to be higher in the bosentan group (Fig. 1). Although the difference was not as marked, our data show a similar trend to STRIDE-2X with respect to transaminase elevation [12]. The event rate we observed with both therapies justifies monthly liver enzyme testing. The continuing decline of haemoglobin levels presented here is not entirely consistent with previous reports that levels stabilize after a few weeks [5]. Many of these patients were on concomitant warfarin, but the known interaction with sitaxentan that increases prothrombin time could not explain the bosentan results or the ongoing decline. Thus, other explanations for this observation in the CTD population need to be considered and the role of anti-coagulation in this group should be properly assessed. We did not formally assess drug interactions, although many patients were given concomitant sildenafil, reflecting current therapeutic trends. In pharmacokinetic studies, when bosentan is prescribed with sildenafil, plasma concentrations of the former rise, whereas those of the latter fall [22]. There is no similar interaction between sitaxentan and sildenafil [23]. The combination of sildenafil and sitaxentan is being evaluated in ongoing studies.

Study limitations

This is not a randomized trial, but simply a real-life, prospective audit of current clinical practice, justified by the suggestion of superiority of ETRA selectivity that had been proposed based on limited data from the STRIDE-2X trial. Our goal was to determine whether in our population the substantial benefits suggested in this post hoc trial analysis could be extrapolated into clinical practice. Due to small patient numbers, the power of this study to detect differences between the groups was low. We were also unable to undertake regression analysis of the cohort as a whole, which may have allowed us to uncover any confounders in these complex patients which might account for differences in response to therapy. There may be lead time bias as the sitaxentan group included patients (27%) who had previously used bosentan. Our data in combination with the published data suggest that a comparative trial to demonstrate a difference in treatment effect of these two therapies would need to recruit a large number of patients. With an α-value of 0.05 and powered to 95%, a randomized trial to show a difference between the two strategies would need a total of 210 patients for survival or 134 for clinical worsening based on the STRIDE-2X data. With the results from our study factored in a total of 770 patients would be needed to demonstrate the difference in survival or 218 for clinical worsening.

The present study highlights important issues about CTD-PAH and ETRAs. Bosentan and sitaxentan improve haemodynamics, but improvements in exercise performance and NT-proBNP were not well maintained. We were not able to demonstrate superiority of either ETRAs; formal comparison would require an adequately powered, randomized controlled trial. Encouraging survival outcomes can be achieved in CTD-PAH patients without significant lung disease. However, the substantial clinical worsening rates suggest that further advances in therapy are needed. Finally, based upon our findings, we consider that great caution should be exercised when interpreting post hoc data from clinical trials. Proper comparison of treatment regimens would require adequately powered, double-blind, randomized clinical trials and superiority of one drug over another cannot be robustly explored in any other way. The commercial and logistic challenges for such studies are substantial.

Rheumatology key messages

- Prognosis in CTD-PAH has improved with ETRAs, but clinical worsening rates remain high.
- Neither sitaxentan nor bosentan appears to be superior.
- Monitoring of haemoglobin and transaminases is mandatory for all ETRAs.
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