North East Treatment Advisory Group

Bosentan in the management of digital ulcers

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April 2010

Summary

- Bosentan is oral drug with vasodilatory actions licensed to prevent new digital ulcers in patients with systemic sclerosis. Bosentan is designated an orphan drug.

- Systemic sclerosis is a rare condition characterised by excessive fibrosis of the vasculature and skin resulting in skin thickening, vascular constriction, and eventually organ death. Digital ulcers are a common manifestation resulting from vascular constriction and necrosis in the fingers and toes, causing pain and often amputation.

- Typical management relies upon lifestyle changes and treatment with vasodilator drugs such as calcium channel blockers. More severe cases may require treatment with intravenous prostacyclin analogues in an acute setting.

- Bosentan has been evaluated in two short-term placebo-controlled randomised controlled trials of patients with systemic sclerosis and digital ulcers. The evidence indicates modest and limited efficacy, demonstrating little or no effect on existing ulcers but a reduction in the emergence of new digital ulcers. Small but statistically significant improvements in hand function have also been demonstrated. Longer-term non-comparative data indicate that initial efficacy is maintained.

- Bosentan has a fairly well established adverse effect profile. Liver enzyme abnormalities are common, affecting about 10% of patients and resulting in treatment cessation in about 5%. Other common adverse effects include oedema, fluid retention, anaemia, and gastrointestinal effects.

- Bosentan is an expensive drug with an annual cost in excess of £19,000 per patient. In addition, patients will require monthly liver enzyme function tests. Off-set costs may be substantive if patients are withdrawn from prostacyclin therapy with an attendant reduction in medical care. Conventional oral therapy for digital ulcers and the commonly associated Raynaud's phenomenon are generally of low acquisition cost.

- The prevalence of severe digital ulcer disease with systemic sclerosis is estimated at a mean of about two patients per primary care trust within NHS North East.

Introduction

Bosentan (Tracleer®) is an endothelin receptor antagonist that has been available in the UK for a number of years for the treatment of pulmonary arterial hypertension. Since May 2007 it has also been licensed to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. [1,2] Bosentan is designated as an orphan drug by the European Medicines Agency. [3]

Systemic sclerosis is a multi-system disease principally affecting the skin, digital vasculature, and internal organs. The pathogenesis of systemic sclerosis is not fully understood but appears to involve complex interactions between excessive fibrosis, vascular abnormalities, and abnormalities of the immune system. The key features of systemic sclerosis result from a combination of fibrosis and ischaemic atrophy. The most characteristic fibrotic manifestation is scleroderma (thickening and hardening of the skin) and the most characteristic vascular manifestation is severe Raynaud's phenomenon. However fibrosis and ischaemia of internal organs, which may commence and progress unnoticed, present the greatest risk of mortality. Systemic sclerosis is often complicated by the presence of other conditions with an autoimmune origin such as systemic lupus erythematosus and rheumatoid arthritis. [4,5]

Systemic sclerosis is generally categorised into limited and diffuse disease, descriptors that relate to the extent of skin, or cutaneous, involvement and which also indicate the severity and propensity of certain aspects of the condition. Limited disease is generally associated with more severe vascular manifestations (e.g. severe Raynaud's phenomenon) compared with more pronounced fibrotic manifestations with diffuse disease (e.g. widespread skin thickening). [5]

The main presenting symptoms of systemic sclerosis are Raynaud's phenomenon and pulmonary arterial hypertension, the latter being a potentially life-threatening complication. [5]

Raynaud's phenomenon is characterised by poor blood flow to the extremities, especially the fingers and toes (digits) and is a common complication of systemic sclerosis affecting up to 95% of patients. In patients with Raynaud's phenomenon secondary to systemic sclerosis the symptoms will usually progress to become more severe, resulting in pain, ulceration and tissue necrosis. Multiple digits may be affected at any one time with varying degrees of severity. Other complications may also occur such as digital 'pits' (depressions), whole-digit ischaemia, gangrene, and autoamputation. Surgical amputation of digits is sometimes required. [5,6]

The treatment of Raynaud's phenomenon and digital ulcers secondary to systemic sclerosis is similar. Patients are advised not to let the digits get cold so as to maintain blood supply and, if relevant, to cease smoking, with both measures associated with improved symptom control. If treatment is indicated

the first-line option is usually a calcium channel blocker (vasodilator), most often nifedipine. For digital ulcers specifically, prostacyclin analogues, especially iloprost, are also recommended. Prostacyclin analogues must be administered parenterally and over relatively long periods of time per cycle of treatment although there may be relatively long periods between cycles. [5-9]

Other treatments used in the management of systemic sclerosis but not specifically digital ulcers may also have positive effects on digital aspects. Examples of these treatments include renin-angiotensin system vasodilators, particuarly the angiotensin converting enzyme inhibitors captopril and enalapril; sildenafil, cyclophosphamide, and systemic corticosteroids. Digitial ulcers may necessitate the use of adjuvant treatments such as analgesics including drugs for neuropathic pain, and antibiotics for infective complications. [5-9]

Bosentan is the only treatment available in the UK that is licensed for the treatment of digital ulcers due to systemic sclerosis. [10]

The licensed dose of bosentan in the management of digital ulcers in patients with systemic sclerosis is 62.5 mg twice daily for four weeks, increased to 125 mg twice daily thereafter.[1] The short-term net pharmacological effect of bosentan is vasodilatory. Longer-term effects have not been confirmed but, due to the role of endothelin in numerous pathways and functions such as cell proliferation and death, it may result in some degree of structural change of the vasculature. [4]

The North East Treatment Advisory Group has been requested by an NHS North East acute trust to conduct an appraisal of, and issue a recommendation for, the use of bosentan in the management of digital ulcers. The submission to NETAG has been prompted by a specific case however the group is requested to consider the issues generally.

Complex connective tissue disease and rare conditions, including ‘complex vasculitis and complex scleroderma’ are included in the second edition of the national specialised commissioning definition set number 26, Specialised Rheumatology Services (Adult). Currently, services for systemic sclerosis (excluding pulmonary arterial hypertension) are not commissioned by the North East Specialised Commissioning Team. [11]

Clinical Evidence

The key sources of evidence for the use of bosentan in the management of digital ulcers is a pair of randomised, double-blind, placebo-controlled trials known as RAPIDS-1 and RAPIDS-2.[A] The latter has not yet been fully published although some preliminary results are available.

In RAPIDS-1 (n = 122), 79 patients were treated with bosentan (62.5 mg twice daily for four weeks, then 125 mg twice daily for 12 weeks) and 43 with placebo for 16 weeks. Patients had a confirmed diagnosis of systemic sclerosis, a mean age of 52 years (minimum 18 years), and were predominantly white (94%) and female (79%). About 60% had limited disease and 40% diffuse disease, with mean disease duration of about 9 years. The primary outcome measure was the number of new digital ulcers that developed during the treatment period. This demonstrated a significant difference between treatments with a mean of 1.4 new ulcers per patient with bosentan and 2.7 with placebo (p = 0.0083). The difference was greater in patients who had ulcers at baseline (63%) and in those with diffuse disease. Indeed, a subgroup analysis by disease presentation revealed that the effects were not significant for those with limited disease. Other outcome measures included temporal healing and emergence effects and a qualitative assessment of manual function. The general trend was for small but significantly beneficial effects for bosentan over placebo. Key results are displayed in table 1. [12]

A twelve week open label extension of the RAPIDS-1 study has been reported in abstract only. Eighty-eight patients entered this extension study, 31 who had previously received treatment with placebo and 57 with bosentan. A total of 62 new ulcers were experienced by 88 patients resulting in a mean 0.7 new ulcers per patient. Mean changes in health assessment score (disability index) and hand function score, and visual analogue scale assessments of symptoms, all demonstrated small improvements over the 12 week study duration. [13]

Results from the RAPIDS-2 study are only available in abstract or from review articles. Patients were randomised to treatment with bosentan (62.5 mg twice daily for four weeks, then 125 mg twice daily for an additional 20 to 32 weeks [n = 98]) or placebo (n = 90). Patients had at least one current or a recent past history of digital ulcer, a mean age of about 50 years (minimum 18 years), and were predominantly female (~80%) and white (~85%). About 40% had diffuse disease with the remainder having limited disease. Mean disease duration was 8.7 years, with a mean of 3.6 ulcers per patient at baseline. The 'co-primary' outcome measures were time to complete healing of the cardinal ulcer and the number of new ulcers emerging during the first 24-weeks of the study. Key outcomes are displayed in table 1. The results indicated that bosentan was more effective in patients with more severe disease indicated by the presence of at least three ulcers at outset. [14]

[A] The acronym RAPIDS stands for 'RAndomized [sic] Placebo-controlled study on prevention of Ischemic [sic] Digital ulcers in Scleroderma'

Table 1: Summary of key results of the RAPIDS studies.

Outcome	Bosentan			Placebo		
	All	Diffuse	Limited	All	Diffuse	Limited
RAPIDS-1						
Proportion with ulcers at baseline	67%	73%	64%	56%	50%	61%
Mean number of ulcers at baseline	1.9	2.2	1.8	2.2	2.2	2.1
Mean number of new ulcers after 16 weeks	1.4			2.7		
Mean number of new ulcers after 16 weeks in patients with ≥ 1 ulcer at baseline	1.8			3.6		
Proportion experiencing new ulcers	58%			61%		
Proportion of patients with no new ulcers	~30%			~30%		
Proportion of patients with no healing of baseline ulcers	~20%			~20%		
Time to complete healing of baseline ulcers	No significant difference					
Time to onset of new ulcers	No significant difference					
Mean scores for components of the Scleroderma Health Assessment Questionnaire relating to hand function, as well as the composite score for the three components (approximate results)						
Dressing/grooming	- 0.1			+ 0.20	p = 0.02	
Hygiene	- 0.1			+0.25	p = 0.03	
Grip	- 0.1			+ 0.15	p > 0.05	
Composite: hand function	- 0.1			+ 0.20	p < 0.005	
RAPIDS-2						
Mean number of new ulcers over 24 weeks	1.9			2.7	p = 0.035	
Proportion of patients with complete healing of cardinal ulcer at 24 weeks	37%			39%		
Mean number of new ulcers over 24 weeks; baseline ≤ 3 ulcers	1.4			1.9		
Mean number of new ulcers over 24 weeks; baseline ≥ 4 ulcers	2.3			4.4		
Mean scores for items of the Scleroderma Health Assessment Questionnaire – Disability Index (approximate results)						
Eating	- 0.10			+ 0.10		
Dressing	- 0.35			+ 0.05		
Change in functional assessment score	No significant difference (p = 0.312)					

Longer-term evidence

Evidence for the use of bosentan for the treatment of digital ulcers over the longer-term is available from three case-series reports.

Tsifetaki et al report their experiences gained from use of bosentan in 26 patients (mean age 60 years, 22 were female, mean disease duration 12.5 years) for up to three years. Sixteen patients had limited disease and 10 had diffuse disease, and all were refractory to previous treatments although there was a relatively high rate of use of other drugs during the study. They report that the mean number of digital ulcers showed continual gradual decline over the entire study period from nearly six at baseline to less than four after three years, a decrease of about two ulcers. Healing of pre-existing ulcers occurred in 17 patients after a mean period of 25 weeks. New ulcers developed in five patients. [15]

In another report a Spanish team describe their experiences of using bosentan in 15 patients (mean age 48 years, range 11 to 72, 12 female, mean disease duration 14.5 years) with a median follow-up of 25 months (range 4 to 36). Results are calculated relative to baseline per patient. After one year a significant improvement was observed in the mean number of ulcers, episodes and duration of Raynaud's phenomenon, and some patient reported assessments. These effects were maintained at 18 months although no changes were found in qualitative assessments of functional performance or disease impact. After two years further improvements were noted in other parameters although there was a worsening in hand extension. Only five patients had follow-up beyond two years. [16]

A report of 15 patients treated with bosentan for pulmonary arterial hypertension included eight patients with between one and five digital ulcers (mean of two) at baseline (six were female, mean age 54 years). Two of the eight patients were described as having mixed connective tissue disease, and six with systemic sclerosis. Follow-up was 24 months except for two patients who died from unrelated causes at 11 and 15 months. In all eight patients with digital ulcers healing was evident at a median of 12 weeks after start of treatment (range six to 14) and no patients developed new digital ulcers. Complete healing occurred in six patients after a median of 20 weeks (range 16 to 24). [17]

Quality of life evidence

Quality of life data from a subset of 15 patients with digital ulcers and receiving treatment with bosentan for pulmonary arterial hypertension has been reported in abstract. Results were obtained at study end (48 weeks or earlier if withdrawn) and include the short form 36 (SF36) score (range 0 to 100) and visual analogue scale (VAS) scores of the sceleroderma health assessment questionnaire (a disease specific questionnaire, VAS range 0 to 3). The mean change in SF36 score from baseline demonstrated an improvement of 5.7 points. Mean changes in VAS score from baseline also demonstrated improvements (reductions) of 0.25 for pain, 0.22 for vascular disease, 0.43 for ulceration, and 0.02 for overall disease severity. [18]

Summary of the clinical evidence

It is unfortunate that the RAPIDS-2 study, probably the most pertinent to the clinical use of bosentan for digital ulcers and with the greatest number of patients and longest duration, is only due for publication later in 2010 despite results being first presented in 2006. In recommendations for the treatment of systemic sclerosis from the European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research Group (EUSTAR), the summary of evidence for bosentan for digital ulcers states: [19]

> "Neither [RAPIDS] trial indicated that bosentan is superior to placebo in the healing of systemic sclerosis-related active digital ulcers, as evaluated by the time to complete or partial healing of digital ulcers present at baseline, the time to healing of all digital ulcers, or the percentage of patients with complete digital ulcer healing ($p > 0.05$ vs placebo for all comparisons). The beneficial effect on new digital ulcer formation was accompanied by a significant improvement in overall hand function (specific health assessment questionnaire (HAQ) score ES 0.4; 95% CI 0.0 to 0.8) in RAPIDS-1, and a significant improvement in the Scleroderma-HAQ dressing domain ($p = 0.03$) in RAPIDS-2."

The recommendation from EUSTAR is: [19]

> "Bosentan has no confirmed efficacy in the treatment of active digital ulcers in systemic sclerosis patients. Bosentan has confirmed efficacy in two high-quality randomised controlled trials to prevent digital ulcers in diffuse systemic sclerosis patients, in particular those with multiple digital ulcers. Bosentan should be considered in diffuse systemic sclerosis with multiple digital ulcers after failure of calcium antagonists and, usually, prostanoid therapy."

In a review of outcome assessment in studies of digital ulcers in scleroderma, the authors, one of whom is a lead investigator of the RAPIDS-2 study, comment: [20]

> "In both [RAPIDS] trials, bosentan was ineffective in healing of established digital ulcers and no effect on Raynaud's phenomenon was shown. Benefit of bosentan was limited to reduction of the occurrence of new digital ulcers (30 to 48%)."

And in addition: [20]

> "In RAPIDS 2 …… the small effect of [bosentan on] prevention [of new digital ulcers] was subsumed by higher rates of healing on placebo. Thus at the end of 24 weeks of drug therapy, there were no differences between active treatment and placebo in net digital ulcer burden, pain, measures of activities of daily living by health assessment questionnaire or UK Functional Score or in hospitalization [sic] rates."

It would appear that the clinical efficacy of bosentan in the management of digitial ulcers is limited to reducing the number of new ulcers over a relatively short period with a small effect on hand function, again only demonstrated over a relatively short period. There is no evidence as to whether these differences are

maintained in the longer term. There is an indication that efficacy is greatest in patients with active multiple ulcers, and diffuse systemic sclerosis disease although this has not been convincingly demonstrated. There is very limited evidence of the longer-term effects of bosentan in managing digital ulcers.

Safety

Bosentan has been available in the UK since about 2002 and in other markets prior to that. The Medicines and Healthcare Products Regulatory Agency had received 57 reports of 144 adverse reactions or effects associated with bosentan between June 2002 and January 2010. Five reports included a fatality. The most commonly affected 'system organ class' was 'investigations' with 38 reports, the majority relating to liver enzyme results. Note that causation is not confirmed in any of these cases and the majority of this use is unlikely to have been for digital ulcers. [18]

The product data-sheet lists liver test function abnormalities, oedema, and fluid retention as being associated with an incidence of at least 10% in placebo-controlled studies of digital ulcers. The data-sheet also states that liver function should be monitored prior to treatment and then monthly regardless of indication or dose. In addition, an algorithm details the actions required depending on specific enzyme results and non-specific symptoms that may be indicative of liver damage. [1]

In the RAPIDS-1 study the most common adverse effects in bosentan and placebo groups, respectively, were; headache (both ~16%), liver function test abnormality (11% and 0%), respiratory infection (9% and 14%), vomiting (both 9%), diarrhoea (9% and 2%), infected skin ulcer (8% and 5%), and arthralgia (6% and 16%). Five patients experienced a serious adverse event (two with bosentan). Six per cent of bosentan-treated patients had treatment discontinued due to liver function abnormalities and in total nine (11%) bosentan patients ceased treatment for adverse effects. [12]

Safety results from the RAPIDS-2 study are currently poorly reported. Aspartate and alanine aminotramsferase levels of at least three times the upper normal limit were observed in 11% of bosentan and 1% of placebo patients. [14]

Safety results from the longer-term studies are poorly described. In the larger study with 26 patients, three patients discontinued treatment, two due to raised liver enzymes and one due to reduced blood cell count. In the Spanish report with 15 patients treatment was discontinued in one due to toxic jaundice which later resolved. In two other cases treatment was temporarily discontinued due to hepatic complications and three patients showed mild transitory raised liver enzymes. Other notable effects include two reports of anaemia and six reports of non-anaemic decreases in haemoglobin. [15,16]

Cost analysis

Bosentan (Tracleer®) is available in tablets of 62.5 mg and 125 mg, in packs of 56, each sufficient for 28 days treatment and each costing £1,467.65 per pack. Therefore the annual cost of treatment per patient is £19,079. These costs do not include VAT which is payable on all medicines provided via acute hospital trusts. The annual cost per patient including VAT is £22,418, or £1,724 per pack. VAT is not payable on medicines provided by primary care dispensing contractors or via 'homecare' arrangements. [22] Primary care prescribing data indicates that bosentan is seldom prescribed outside of the acute sector with only two prescriptions recorded within NHS North East during 2009. [23] Cost of provision of bosentan via homecare arrangements is about £[redacted] per annum. [24]

It has not been possible to calculate or estimate a cost per quality adjusted life year (QALY) with bosentan because evidence for its effect on overall quality of life was not sufficiently robust. Evidence does indicate that, with respect to functional changes, bosentan produces small and statistically significant benefits. Functional ability is just one component of a quality of life measure and the overall effect on quality of life from this alone is likely to be small.

As stated in the EULAR and EUSTAR recommendations, iloprost should be considered prior to initiation of bosentan.[19] This represents an off-license indication and as such there are no licensed dose instructions. The following dose schedule is taken from a key clinical study: 2 ng/kg/min for five consecutive days for eight hours per day and then for eight hours on one day every six weeks. [20] For a 60 kg adult, this would correspond to an annual consumption of nearly 800 micrograms requiring a total of twelve 100 microgram vials. The associated drug cost is £1,127 including VAT. However, it is likely that non-drug costs would account for the majority of the costs of using iloprost as the following would be required as a minimum:

- Permanent intravenous access
- Administration equipment which will require close monitoring
- Preparation of injections and apparatus requiring skilled labour
- Five-day inpatient stay
- Nine subsequent outpatient or day case visits with a suitable residual observation period

Some of these are non-recurring costs or costs that may recur only infrequently and unpredictably. Example costs are:[B] [26]

- Admission for 'vascular access except for renal replacement therapy without complications or co-morbidities': £747
- In-patient stay of up to eight days for 'musculoskeletal or connective tissue disorders': £1,348
- Planned day-case admission for 'musculoskeletal or connective tissue disorders without complications or co-morbidities': £608

[B] These figures do not include the uplift multiplier, known as the 'market forces factor' which is typically between 2 and 3.5% for trusts within NHS North East [22]

The tariff price includes labour and hardware costs but not the cost of iloprost. [27] Therefore, using these values, the cost of administering iloprost according to the stated schedule would be £8,694 in the first year. If bosentan therapy requires only the minimum of two outpatient appointments per annum (one for initiation and one for up-titration) and provision is VAT exempt (both favourable to the overall cost) the incremental cost of bosentan over iloprost is about £11,000 for the first year of therapy. At this cost bosentan would need to demonstrate an improvement in QALYs of at least 55% over treatment with iloprost to meet conventional NHS cost-effectiveness thresholds. There is no evidence that bosentan has any impact on survival and the evidence on quality of life alone indicates that a change of this magnitude is highly unlikely.

Liver function tests are recommended at least monthly throughout treatment and more frequently if deranged results are obtained. The cost of a standard liver function test has been estimated at £4.12, therefore the annual cost of liver function tests for patients on bosentan is about £50. [28] This cost has not been included in the above analyses as it is small relative to total drug cost.

A report published in 2004 measured the prevalence of systemic sclerosis in a population derived predominantly from Newcastle and Northumberland. This is also the most recent estimate of the prevalence of systemic sclerosis from a UK-based population. The prevalence of systemic sclerosis in this study was found to equate to 8.8 per 100,000 population, with a female bias of 5.2:1 and a limited to diffuse disease bias of 4.7:1. Transposing this data to the whole of NHS North East yields an estimated patient population of 225. [29]

Epidemiological data, published in abstract only, reports the outcomes from 2,080 patients with systemic sclerosis followed prospectively for a mean of 10 years. Persistent digital ulcers, defined as persistent or recurrent for at least six months, were observed in 666 patients (32%). Severe ulcers were defined as those with gangrene or requiring nerve excision or amputation and occurred in 197 patients (9.5%). [30]

A prospective study of 281 adult patients with systemic sclerosis and severe symptoms of Raynaud's phenomenon found that 21% of patients had incident digital ulcers at baseline. [31] More recent prevalence data obtained from a UK centre found that of 203 systemic sclerosis patients with symptoms indicating severe vasculopathy, 17% developed ≥ 1 new digital ulcer during 18 months. [32]

If the higher prevalence rate of 32% is combined with the estimated patient population for NHS North East [33] this yields an estimated 72 patients with persistent and 22 patients with severe digital ulcers. The potential annual cost of treatment is calculated for each primary care trust with data adjusted for the size of GP-registered populations (table 2).

Table 2. Estimated patient population of digital ulcers with systemic sclerosis and annual cost of treatment with bosentan

(Primary Care) Trust	% Registered patient population NHS North East	Persistent systemic sclerosis with digital ulcers**		Severe systemic sclerosis with digital ulcers***	
		Estimated number of patients*	Annual drug cost	Estimated number of patients*	Annual drug cost
Newcastle	10.2%	8	£152,632	3	£57,237
North Tyneside	8.0%	6	£114,474	2	£38,158
Northumberland Care	12.2%	9	£171,711	3	£57,237
Total			*£438,817*		*£152,532*
County Durham	19.9%	15	£286,185	5	£95,395
Darlington	3.8%	3	£57,237	1	£19,079
Total			*£343,422*		*£114,474*
Gateshead	7.6%	6	£114,474	2	£38,158
South Tyneside	5.9%	5	£95,395	2	£38,158
Sunderland Teaching	10.7%	8	£152,632	3	£57,237
Total			*£362,501*		*£133,553*
Hartlepool	3.6%	3	£57,237	1	£19,079
Middlesbrough	5.6%	4	£76,316	2	£38,158
North Tees	7.4%	6	£114,474	2	£38,158
Redcar and Cleveland	5.2%	4	£76,316	2	£38,158
Total			*£324,343*		*£133,553*
NHS North East		77	£1,469,083	28	£534,212

* : Values relating to estimated patient numbers have been rounded up to the next integer.
** : It is assumed that the prevalence of digital ulcers in patients with systemic sclerosis is about one-third. [30]
*** : It is assumed that about 10% of all patients with systemic sclerosis will have severe symptoms of digital ulcers. [30]

Points to consider

- The evidence for bosentan indicates that it is able to retard, and possibly prevent, the development of new digital ulcers in patients who already have digital ulcers. This evidence has been derived from relatively short-term placebo-controlled studies. The evidence does not demonstrate that it can result in healing of existing ulcers or change the course of the underlying condition. Long-term comparative evidence does not exist. Long-term case series indicate that initial efficacy is maintained.

- There is evidence that bosentan, when used for the treatment of digital ulcers, results in small but significant improvements in quality of life scores relating to hand function and dexterity.

- Elevated liver function test results are relatively common, affecting about 10% of patients and leading to cessation of treatment in about half of those patients (i.e. 5% overall). Patients must have their liver function monitored at least monthly whilst taking bosentan.

- Actelion Pharmaceuticals is collating post-marketing surveillance data specifically enrolling patients with systemic sclerosis and digital ulcers. Currently this has data relating to 1,600 patients from the European Union with digital ulcers and systemic sclerosis. About 10% of these patients are being treated with bosentan for digital ulcers, a similar rate to that estimated to experience severe symptoms. [27] Actelion supports the use of bosentan principally for patients with severe (defined as ≥ 3 digital ulcers) ongoing disease and who have had at least two courses of iloprost in the preceding 12 months.

- Bosentan is a costly drug with an annual cost in excess of £19,000. For the management of digital ulcers alone it is unlikely to meet conventional limits for cost-effectiveness in terms of cost per quality adjusted life year. Bosentan is often considered as an alternative to iloprost, itself a costly treatment that must be administered under medical supervision in an acute setting.

- Bosentan is likely to be a more convenient treatment option compared with iloprost due to oral tablet formulation although patients must undergo regular liver function monitoring.

Author's declaration: The author has no relevant interests to declare.

References

1. Tracleer®▼ (Actelion Pharmaceuticals). Summary of product characteristics. Accessed via http://emc.medicines.org.uk, February 2010.
2. Anon. SPC changes, prescription products, products miscellany. Pharmaceutical Journal 2008;280:650
3. European Medicines Agency. Committee for Orphan Medicinal Products. Public summary of positive opinion for orphan designation of bosentan. Document reference EMEA/COMP/270/03 Rev.1. May 2007
4. Gabrielli A, Avvedimento EV, Krieg T. Mechanisms of disease: Scleroderma. New England Journal of Medicine 2009;360(19):1989-2003
5. Herrick AL. Systemic sclerosis: an update for clinicians. British Journal of Hospital Medicine 2008;69(8):464-70
6. Pope JE. The diagnosis and treatment of Raynaud's phenomenon: A practical approach. Drugs 2007;67(4):517-25
7. Dhillon S. Bosentan: A review of its use in the management of digital ulcers associated with systemic sclerosis. Drugs 2009;69(14):2005-2
8. Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. Arthritis and Rheumatism 2001;44(8):1841-7
9. Pope J, Fenlon D, Thompson A, Shea B et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database of Systematic Reviews 1998, issue 2. DOI: 10.1002/14651858.CD000953
10. Electronic medicines compendium. www.medicines.org.uk/emc Accessed April 2010
11. Specialised services national defintions set (2nd edition). Specialised rheumatology services (Adult) – definition no. 26.
12. Korn JH et al. Digital ulcers in systemic sclerosis: Prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis and Rheumatism 2004;50(12):3985-93
13. Black C, Denton CP, Furst DE et al. Bosentan reduces the number of new digital ulcers in patients with systemic sclerosis – open label extension to a double-blind trial. Annals of Rheumatic Diseases 2006;65(S2):384
14. Seibold JR et al. Bosentan prevents occurrence but does not speed healing of digital ulcers in patients with systemic sclerosis (SSc). Poster (L2: 552) presented at the American College of Rheumatologists, November 2005
15. Tsifetaki N et al. Bosentan for digital ulcers in patients with systemic sclerosis: A prospective 3-year followup study. Journal of Rheumatology 2009;36(7):1550-1
16. Garcia de la Pena-Lefebvre P et al. Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients. Rheumatology 2008;47(4):464-6
17. Funauchi M, Kishimoto K, Shimazu H et al. Effects of bosentan on the skin lesions: an observational study from a single center in Japan. Rheumatology International 2009;29(7):769-75
18. Denton CP, Gabrielli A, Peter H et al. Long-term effects of bosentan on quality of life (QOL) and survival, in patients with pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD): A subgroup analysis of patients with digital ulcers. Annals of Rheumatic Diseases 2007;66(S2):208

19. Kowel-Bielecka O et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Annals of Rheumatic Diseases 2009;68:620-8
20. Matucci-Cerinic M, Seibold JR. Digital ulcers and outcomes assessment in scleroderma. Rheumatology 2008;47:v46-7
21. Anon. Drug analysis print: Bosentan. Medicines and Healthcare Products Regulatory Agency. www.mhra.gov.uk/Onlineservices/Medicines/Druganalysisprints/index.htm Accessed February 2010
22. NHS dictionary of medicines and devices. www.dmd.nhs.uk Accessed February 2010.
23. Data provided by the Regional Drug and Therapeutics Centre (Newcastle). February 2010.
24. Data on file. North East Specialised Commissioning Team. July 2009
25. Scorza R et al. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon. A randomized, controlled study. Clinical and Experimental Rheumatology 2001;19(5):503-8
26. Payment by results tariff for hospital episodes of care 2009-11
27. Department of health. Payment by results tariff for 2010-11. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_112284
28. Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, Rosenberg W. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). Health Technology Assessment 2009;13:25
29. Allcock RJ, Forrest I, Corris PA, Crook PR, Griffiths ID. A study of the prevalence of systemic sclerosis in northeast England. Rheumatology 2004;43:596-602
30. Ingraham KM, Steen VD. Morbidity of digital tip ulcerations in scleroderma. Abstract number 578, American College of Rheumatology 2006.
31. Merkel PA et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis and Rheumatism 2002;46(9):2410-20
32. Nihtyanova SI et al. Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. Annals of Rheumatic Diseases 2008;67:120-3
33. The Information Centre for health and social care (NHS). Attribution dataset GP registered populations 2008. www.ic.nhs.uk/statistics-and-data-collections/population-and-geography/population/attribution-dataset-gp-registered-populations-2008