Author's response to reviews

Title: A case report of the effect of the dual endothelin receptor antagonist, bosentan, on untreated ulcers in a diabetic patient

Authors:

Fatima Álvarez Reyes Dr (falvrey@gmail.com)
Cristina Luna Gómez Dr (cristinaluna76@gmail.com)
Manuel Brito Suárez Dr (mbrisua@gobiernodecanarias.org)

Version: 3 Date: 22 September 2010

Author's response to reviews: see over
Professor Michael Kidd  
Editor, *Journal Medical Case Reports*

**September 22, 2010**

**MS: 1782225524351901: A case report of the effect of the dual endothelin receptor antagonist, bosentan, on untreatable ulcers in a diabetic patient**

Dear Professor Kidd

We have now addressed all the points and concerns raised by the reviewers as indicated in the table below.

<table>
<thead>
<tr>
<th>Responses to key points of reviewers</th>
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<td>1. ET-1 may be important in development of diabetic microangiopathy. This patient was elderly with major cerebro-vascular damage and congestive heart failure. How can you exclude these conditions as the major causes of the heel ulceration?</td>
<td>We acknowledge that major cerebrovascular damage and congestive heart failure can be contributing factors to the development of ulcers. However, they cannot have caused the ulcer in this case. Firstly, the stroke experienced by this patient only resulted in mild right residual hemiparesis with little or no loss of function and occurred almost 30 years before the first appearance of the heel ulcer. If the stroke had occurred more recently it could have contributed to the development of the ulcer. Secondly, congestive heart failure occurred after the first appearance of the ulcer. The ulcer first appeared in November 2007, worsening due to resulting inactivity. Congestive heart failure occurred in February 2008 and resulted in hospitalization and the further worsening of the ulcer.</td>
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</table>
| 2. Are you sure that the heel-pad is the common site of diabetic foot (more than peripheral sites like the toe tip)? | We don’t believe that we are claiming that the heel-pad is the common site of diabetic foot ulcers. What we are saying is that when ulcers occur on the heel, they are major complications in diabetes that often lead to }
3. You suggest the cause of the congestive heart failure is ischemic heart disease. What are the supportive data for this inference? ECGs, echocardiograms, etc.

No echocardiography was performed in this patient. Three years earlier, ECG of the heart and an ultrasound were performed which indicated increased LV mass, RBB block and EF of 62%.

4. The duration of the heel ulcer is over one year. Please add further details of all medicines used over this time including antibiotics, vasodilators and anticoagulation.

Details of all medications administered to this patient for the duration of his heel ulcer have been given. At the time of first appearance of the ulcer, the patient was already receiving bicalutamide (non-steroidal anti-androgen for prostate cancer), candesartan (anti-hypertensive), furosemide (diuretic), triflusal (anti-coagulation) and calcium dobesilate (vasodilator). These medications were continued throughout the ulcer-specific treatment.

Treatment of the ulcer itself was initiated with oral ciprofloxacin, 500 mg every 12 hours for 2 months, by the patient’s GP. As a result of bacterial susceptibility testing, which isolated *Staphylococcus aureus* and *Escherichia coli*, three months later antibiotic treatment was continued with clavulanic acid plus amoxicillin (875 mg tid) for 15 days. The patient also received pentoxifylline (600 mg bid). General wound care was with weekly gentle mechanical and enzymatic debridement with Iruroxol and Intrasite hydrogel. After a disappointing response, antibiotic treatment was stopped and bosentan was initiated 6 months after the first appearance of the ulcer with complete healing occurring 21 weeks later. The patient was not treated further with antibiotic therapy during the course of treatment with bosentan.

5. In discussion you write only about clinical improvement; please add discussion

Although we feel that this has been covered in the report, we have expanded sections as
regarding the underlying pathophysiology of ET-1 and diabetic vasculopathy.

6. How did you decide the therapeutic dosage of bosentan?

This is a valid question from the reviewer. Bosentan has been shown to prevent the occurrence of new digital ulcers in systemic sclerosis patients with a history of digital ulceration at an initial dose of 62.5 mg bid, uptitrated to 125 mg bid after 4 weeks (reference added, as suggested by one of the reviewers). However, given our patient’s age and history of cardiopathy, a lower dose of 62.5 mg once daily for one week followed by 62.5 mg every 12 hours (bid) was chosen. This point has been added to the manuscript.

7. Please ask a native English speaker to read and review the paper’s grammar.

Language has been reviewed and amended as appropriate.

Responses to editorial requests

8. In keeping with the journal style, please remove the case overview.

Case overview has been removed.

9. In order to protect the patient’s identity, please remove the dates of treatment from the case presentation section.

All dates of treatment have been removed.

10. Please include the ethnicity of the patient in the case presentation section of the manuscript.

The patient was of white Caucasian ethnicity. This information has been added.

11. Please title the consent statement as ‘Consent’.

The statement has been titled as requested.

I am therefore pleased to resubmit the above case report for consideration for publication in *Journal Medical Case Reports*. This manuscript is the first report of the use of a dual endothelin receptor antagonist in the treatment of refractory skin ulcers associated with diabetes. The treatment was successful and provides evidence in support of a role for endothelin in the pathogenesis of skin ulcerations in diabetic patients and illustrates the potential benefit of bosentan treatment.

I believe this manuscript will be of interest to diabetologists, dermatologists and general practitioners given that non-healing skin ulcers are a major problem in diabetic patients and heel ulcers in particular often lead to below the knee amputation. To our knowledge, this is the first report of the successful management of skin ulcers with bosentan in a diabetic patient.
My coauthors and I confirm that this manuscript has not been published before, nor is it under consideration for publication by any other journal, we would however draw your attention to the fact that an abstract based on this case study has been accepted as a poster presentation by the organizers of the 2009 World Congress of the International Diabetes Federation. We also confirm that none of us has any competing interests to declare.

I trust that the manuscript is now acceptable for publication in your journal and I look forward to hearing from you in due course.

Yours sincerely,

Dr Fátima Álvarez Reyes
(on behalf of Dr Christina Luna Gómez and Dr Manuel Brito Suárez)