DRUG POINTS

Severe necrotising leucocytoclastic vasculitis in a patient taking bosentan

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BMJ 2004;329:430

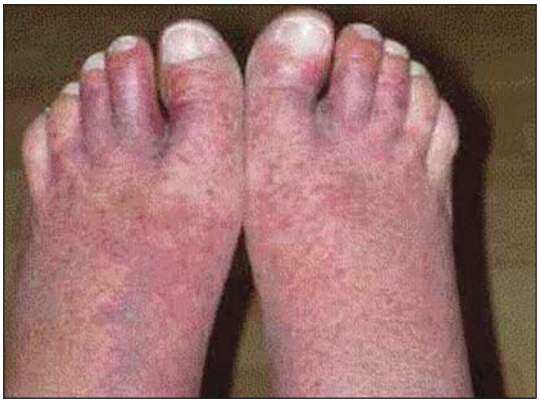
A 47 year old woman had had severe idiopathic pulmonary arterial hypertension since 1988. The patient declined treatment with prostanoids or lung transplantation. Her clinical course was extraordinarily stable with merely acenocoumarol and metolazone.

In June 2002 right heart catheterisation was performed (mean pulmonary arterial pressure 68 mm Hg, cardiac index 2.0 l/min/m^2, mixed venous oxygen saturation 51%, no vasoreactivity). Treatment with bosentan 62.5 mg twice daily was started, and spironolactone was added. Four weeks later, the patient could walk a distance of 380 metres in six minutes, compared with 338 metres before treatment. The bosentan dosage was increased to 125 mg twice daily. Four days later the patient experienced itching of both legs. Within another three days typical vasculitic skin lesions appeared on both legs (figure). A skin biopsy showed leucocytoclastic vasculitis and negative immune complex staining. Haematology, blood chemistry, and immunological variables were unremarkable. Bosentan was stopped immediately. Diuretics and acenocoumarol were continued. The vasculitic skin lesions improved slowly over the following weeks.

Bosentan is an endothelin receptor antagonist approved for the treatment of pulmonary arterial hypertension.[1 2] On the basis of a review of the data from the World Health Organization and the manufacturer's safety database we found that vasculitis has not been reported so far.[3 4] Known side effects of the drug include liver toxicity, which was not present in this case. Vasculitis is well described as an adverse drug reaction to metolazone. This drug, however, had been used by our patient for years, and the vasculitis improved despite the continuation of metolazone.

History and immunology evaluation showed no other causes of the vasculitis, and the skin changes improved after discontinuation of bosentan (positive de-challenge). A re-challenge to corroborate coherency was not considered feasible because of the severity of the skin disorder.

The vasculitic skin lesions in our patient are most probably attributable to bosentan treatment alone or to some hitherto unknown interaction. We recommend that clinicians be alert in patients complaining about pruritus and discontinue the drug if a skin rash appears.



Skin biopsy showed leucocytoclastic vasculitis

Contributors: SG collected data and wrote the article. RS and MK were responsible for corrections and advice. SG, RS, and MK were responsible for caring for the patient.

Funding: Department of Internal Medicine, University Hospital Zurich.

Competing interests: RS has been paid by Actelion for giving a speech and part of his study nurse's salary is paid for by the company.

1 Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.

2 Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-23.

3 International database of the WHO Programme for International Drug Monitoring (Uppsala Monitoring Centre). Data provided by Pharmacovigilance Centre, Swissmedic, Swiss Agency for Therapeutic Products.

4 Eight placebo controlled studies of bosentan (bosentan treatment group n=688): BC-15064 (severe congestive heart failure), BD-14884 (intra-venous study in pulmonary arterial hypertension), NC-15018 (severe congestive heart failure), NC-15020 (essential hypertension), NC-15462 (REACH-1, severe congestive heart failure), NN-15031 (subarachnoid haemorrhage), AC-052-351 (pulmonary arterial hypertension), AC-052-352 (pulmonary arterial hypertension). Further details on these studies are available from the manufacturer of bosentan, Actelion Pharmaceuticals, Allschwil, Switzerland www.fda.gov/ohrms/dockets/ac/01/slides/3775s2_01_actelion.ppt (accessed 14 Apr 2004).

(Accepted 8 December 2003)

An actor's sense of timing

He was an elderly professional actor, and one of my favourite patients. He was nearly as interested in the world of general practice as I was in his theatrical tales. I think we each found the other's work fascinatingly exotic. Once I asked him to return the next day for an appointment at 10 30.

"Certainly," he said, "am or pm?"

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