ESC European Society of Cardiology

European Heart Journal - Case Reports (2021) **5**(12), 1–7
https://doi.org/10.1093/ehjcr/ytab506

CASE SERIES
Heart failure

Who 'nose', is it the angiotensin receptor neprilysin inhibitor?: a case series of persistent nasal pruritus in heart failure patients receiving sacubitril/valsartan

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Received 26 June 2021; first decision 3 August 2021; accepted 6 December 2021; online publish-ahead-of-print 11 December 2021

Background Sacubitril/valsartan is approved for the treatment of chronic heart failure with reduced left ventricular ejection fraction of ≤40% to decrease mortality and morbidity. Nasal pruritus is not a recognized adverse effect in the product information. In this case series, we encountered three patients who presented with nasal pruritus that improved after discontinuation of sacubitril/valsartan.

Case summary Three patients aged 58–73 years-old presented with pruritus at the nasal septum post-initiation of sacubitril/valsartan. The pruritus did not subside despite the use of anti-histamines. Within 3–6 months, all individuals discontinued sacubitril/valsartan with complete resolution of their nasal pruritus.

Discussion Many physicians may not aware of this unusual but reversible adverse effect of sacubitril/valsartan. Despite the positive prognostic value of sacubitril/valsartan, the constant nasal pruritus had impacted the quality of life of our patients, leading them to discontinue sacubitril/valsartan permanently.

Keywords Sacubitril/valsartan • Entresto • ARNi • Nasal pruritus • Allergy • Case series

ESC Curriculum 6.2 Heart failure with reduced ejection fraction • 9.9 Cardiological consultations

Learning points

- Commencement of sacubitril/valsartan coincided with rare side effect of persistent nasal pruritus, but reversible upon cessation of the drug.
- The constant nasal pruritus and the associated impact on the quality of life and mood disturbances, prompted patients to discontinue sacubitril/valsartan permanently.

Introduction

Sacubitril/valsartan is the first agent to be approved in a new class of medications called angiotensin receptor neprilysin inhibitor (ARNi). The medication is efficacious in reducing mortality and morbidity for the treatment of heart failure with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction (LVEF) ≤40%, when compared with standard therapy with angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker.[1] It is well known

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Handling Editor: Dejan Milasinovic
Peer-reviewers: Marta Cvijic and Constantinos Bakogiannis
Compliance Editor: Reshma Amin
Supplementary Material Editor: Fabienne Vervaat

that ACE inhibition causes accumulation of bradykinin in the airways, which may contribute to the development of a dry cough. Bradykinin is metabolized by many different peptidases. Peptidase inhibitor therapies, such as ACEi and neprilysin inhibitors, increase bradykinin levels (*Figure 1*).[2] Accumulation of bradykinin may cause inflammation and angio-oedema.[2] As such, sacubitril cannot be used with an ACEi, due to an increased risk of angio-oedema from bradykinin accumulation. When switching between ACEi and sacubitril/valsartan, the patient must undergo a 36-h washout period to lower the risk of angio-oedema.[1,2]

There are some case reports of ACEi-induced nasal blockage, rhinitis, and postnasal drainage that improved after discontinuation of ACEi and substitution with angiotensin II receptor blockers.[3] Little is known with sacubitril causing upper respiratory symptoms. In this anecdotal case series, we aimed to describe three individual cases of new-onset nasal pruritus, which temporally coincide with the initiation of sacubitril/valsartan. All three cases were being reviewed routinely in the multidisciplinary heart failure clinic at The Prince Charles Hospital, Brisbane, Australia.

Timeline

Case	Age (years)	Gender	Initial ejection fraction (%)	Sacubitril/valsartan (Sac/Val) initiating dose	Time from initiating Sac/Val to decision of ceasing	Ejection fraction (%) at time of cessation	Pharmacological treatment	Resolution of nasal pruritis upon cessation of Sac/Val	Patient consent to rechallenge Sac/Val
1	69	Male	39%	49/51 mg	3 months	49%	Anti-histamine	Yes	No
2	73	Female	18%	24/26 mg	4 months	47%	Anti-histamine	Yes	No
3	58	Female	21%	24/26 mg	6 months	39%	Anti-histamine	Yes	No

Case presentation

Case 1

A 69-year-old male with chemotherapy-induced cardiomyopathy, despite maximally tolerated medications (*Table 1*) and cardiac resynchronization therapy, presented with New York Heart Association (NYHA) of II and LVEF of 38% [index left ventricular end-diastolic volume (LVEDV) = 90 mL/m^2]. He was commenced on sacubitril/valsartan (49/51 mg) during a routine clinical review.

No known atopy, asthma or allergic rhinitis was documented at baseline. Other past medical histories include: type II diabetes mellitus, obstructive sleep apnoea, ex-smoker, previous pulmonary embolism, left tonsillar, and tongue cancer treated with chemo-radiotherapy.

Known adverse drug reactions include diphenoxylate/atropine causing rash and trimethoprim/sulfamethoxazole causing dizziness. At a routine review 3 months after commencement of ARNi, the patient reported concern of nasal pruritus at the nasal septal area. The patient attributed the pruritus to the start of sacubitril/valsartan 49/51 mg twice daily, which occur within a week. Despite regular anti-histamine and a trial of decreasing the dose of sacubitril/valsartan to 24/26 mg twice daily, the nasal pruritus remained. Upon cessation of sacubitril/valsartan (and changing to ramipril), the nasal pruritus immediately resolved.

Case 2

A 73-year-old female with ischaemic cardiomyopathy (NYHA III; LVEF 18%; index LVEDV 143 mL/m^2) was commenced on low-dose sacubitril/valsartan (24/26 mg) after previously being on ramipril without known adverse reaction. The patient's long-term anticoagulation for secondary prevention of deep venous thrombosis (DVT) was also changed from warfarin to apixaban at the same encounter (*Table 1*).

Patient's past medical history includes coronary artery bypass, chronic obstructive pulmonary disease (smoker), type II diabetes mellitus, infra-renal abdominal aortic aneurysm, chronic back pain, and Hashimoto thyroiditis. Her adverse drug reactions were penicillin/cephalosporin causing hives, atenolol associated bronchospasm, and statins-related myalgia and visual disturbances.

The patient reported constant nasal pruritus within days after the commencement of sacubitril/valsartan and apixaban. Despite reassurance and trial of an empirical oral anti-histamine, the patient self-discontinued both sacubitril/valsartan and apixaban after 4 months with the resolution of nasal symptoms. On review 2 months later at the clinic, the patient was adamant in not re-trialling sacubitril/valsartan despite a documented improvement of symptoms (NYHA III to II) and reverse remodelling of her left ventricle (LVEF from 18% to 47% just prior to ARNi discontinuation). The patient was recommenced on ramipril, and aspirin was used for secondary thromboembolic prevention (no DVT > 12 months). There has been no recurrence of nasal symptoms since the cessation of ARNi.

Case 3

A 58-year-old female with idiopathic dilated cardiomyopathy and NYHA II HFrEF (ejection fraction 21%; index LVEDV 201 mL/m^2) was commenced on sacubitril/valsartan.

Past medical history includes type II diabetes mellitus, chronic obstructive pulmonary disease, hypertension, gastro-oesophageal reflux disease, spinal osteoarthritis, and is a current smoker. History of atopy and multiple known adverse drug reactions and intolerance were documented, including ramipril associated urticaria (*Table 1*).

Table 1 Patient's medication lists and adverse drug reactions

Case 1:

Clinic 07 December 2018—medication list (commencement of sacubitril/valsartan)

***Adverse drug reactions*: diphenoxylate/atropine—rash; trimethoprim/sulfamethoxazole—dizzy.**

Frusemide 40 mg	Take ONE tablet morning and midday.	New
Potassium chloride sustained released 600 mg	Take ONE tablet morning and midday.	New
Sacubitril-valsartan 49 mg/51 mg	Take ONE tablet morning and night.	New—to commence on 10 December 2018
Bisoprolol 10 mg	Take HALF a tablet in the morning.	Unchanged
Aspirin 100 mg	Take ONE tablet in the morning.	Unchanged
Metformin 1000 mg	Take ONE tablet twice a day.	Unchanged
Ascorbic acid	Take ONE daily when required.	Unchanged
Calcium—magnesium—magnesium trisilicate	Chew ONE tablet daily as required.	Unchanged
Ramipril 5 mg	Take ONE tablet morning.	Ceased—changed to sacubitril/valsartan

Clinic 21 March 2019—Medication list (cessation of sacubitril/valsartan)

Ramipril tabs 5 mg	Take ONE tablet morning.	New—to commence on 24 March 2019
Frusemide 40 mg	Take ONE tablet morning and midday.	Unchanged
Potassium chlor sustained released 600 mg	Take ONE tablet twice a day.	Unchanged
Bisoprolol 10 mg	Take HALF a tablet in the morning.	Unchanged
Aspirin 100 mg	Take ONE tablet in the morning.	Unchanged
Metformin 1000 mg	Take ONE tablet twice a day.	Unchanged
Fexofenadine 180 mg	Take ONE tablet daily.	Unchanged
Ascorbic acid	Take ONE daily when required.	Unchanged
Calcium—magnesium—magnesium trisilicate	Chew ONE tablet daily as required.	Unchanged
Sacubitril/valsartan 49/51 mg	Take ONE tablet twice a day.	Ceased—changed to Ramipril

Case 2:

Clinic 17 December 2018—Medication list (commencement of sacubitril/valsartan)

***Adverse drug reactions*: amoxycillin—hives; atenolol—bronchospasm; atorvastatin—visual disturbances; HMG-CoA reductase inhibitors (statins)—myalgia; cephalosporins—hives.**

Apixaban 5 mg	Take ONE tablet twice a day.	New—to commence on 21 December 2018
Nebivolol 5 mg	Take HALF a tablet at night.	New—to commence on 19 December 2018
Sacubitril-valsartan 24 mg/26 mg	Take ONE tablet twice a day.	New—to commence on 24 December 2018
Frusemide (furosemide) 40 mg	Take ONE tablet in the morning.	Unchanged
Potassium chloride sustained released 600 mg	Take TWO tablets in the morning.	Unchanged
Empagliflozin/metformin 12.5 mg/1 g	Take ONE tablet twice a day.	Unchanged
Insulin glargine 100 units/mL	Inject 38 units twice a day.	Unchanged
Fenofibrate tabs 145 mg	Take ONE tablet at night.	Unchanged
Thyroxine (levothyroxine) 50 µg	Take ONE tablet in the morning.	Unchanged
Fluticasone 100 microg/umeclidinium 62.5 µg/vilanterol 25 µg	Inhale ONE dose at night.	Unchanged
Ipratropium 21 µg	Inhale TWO doses four times a day as required.	Unchanged
Salbutamol 100 µg	Inhale TWO doses every four hours as required.	Unchanged
Paracetamol 500 mg	Take TWO tablets four times a day as required.	Unchanged
Magnesium 400 mg	Take TWO capsules daily when required.	Unchanged
Dexchlorpheniramine 2 mg	Take ONE tablet daily when required.	Unchanged
Diazepam 5 mg	Take ONE tablet at night when required.	Unchanged
Warfarin	Variable dosage as directed by your INR blood test.	Ceased on 18 December 2018—changed to apixaban
Aspirin tabs 100 mg	Take ONE tablet in the morning.	Ceased—changed to apixaban
Bisoprolol TABS 2.5 mg	Take HALF a tablet in the morning.	Ceased—changed to nebivolol
Ramipril tabs 2.5 mg	Take HALF a tablet twice a day.	Ceased on 21 December 2018—changed to sacubitril/valsartan

Continued

Table 1 *Continued*

Clinic 13 June 2019—Medication list

Aspirin 100 mg	Take ONE tablet in the morning.	New
Ramipril 2.5 mg	Take ONE tablet twice a day.	Unchanged
Nebivolol 10 mg	Take ONE tablet at night.	Unchanged
Frusemide (furosemide) 40 mg	Take ONE tablet in the morning.	Unchanged
Potassium chloride sustained released 600 mg	Take TWO tablets in the morning.	Unchanged
Empagliflozin/metformin 12.5 mg/1 g	Take ONE tablet twice a day.	Unchanged
Insulin glargine 100 units/mL	Inject 38 units twice a day.	Unchanged
Fenofibrate tabs 145 mg	Take ONE tablet at night.	Unchanged
Ezetimibe 10 mg	Take ONE tablet at night.	Unchanged
Thyroxine (levothyroxine) 50 µg	Take ONE tablet in the morning.	Unchanged
Fluticasone 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg	Inhale ONE dose at night.	Unchanged
Ipratropium 21 µg	Inhale TWO doses four times a day as required.	Unchanged
Salbutamol 100 µg	Inhale TWO doses every four hours as required.	Unchanged
Paracetamol 500 mg	Take TWO tablets four times a day as required.	Unchanged
Magnesium 400 mg	Take TWO capsules daily when required.	Unchanged
Dexchlorpheniramine 2 mg	Take ONE tablet daily when required.	Unchanged
Diazepam 5 mg	Take ONE tablet at night when required.	Unchanged
Colecalciferol (colecalciferol) 25 µg (1000 units)	Take ONE tablet in the morning.	Unchanged

Note: Patient stopped sacubitril/valsartan and apixaban during April 19.

Case 3:

Clinic 21 August 2019—Medication list

***Adverse drug reactions*: amoxycillin/clavulanic acid—hives; beta blockers—abdominal pain; calcium—nausea, pins, and needles; cephalosporin—rash/diarrhoea; clopidogrel—itching; fluticasone furoate—palpitations; fluvoxamine/fluoxetine—diarrhoea; methyldopa—diarrhoea; morphine—vomiting; ondansetron—leg swelling; pantoprazole/esomeprazole—cramps, hypomagnesaemia; quetiapine—rash; ramipril—hives, pins and needles; spironolactone—leg cramps; telmisartan—blurred vision.**

Sacubitril-valsartan 24 mg/26 mg	Take ONE tablet in the morning.	Unchanged
Sacubitril-valsartan 49/51 mg	Take ONE tablet at night.	Unchanged
Nebivolol 10 mg	Take ONE tablet at night.	Unchanged
Frusemide (furosemide) 40 mg	Take HALF a tablet in the morning.	Unchanged
Magnesium	Take ONE tablet in the morning.	Unchanged
Coenzyme Q10	Take ONE capsule in the morning.	Unchanged
Insulin aspartate mix30	Inject when blood sugar level is >12, administer FIVE units daily when required. Give with food.	Unchanged
Paracetamol 500 mg	Take TWO tablets four times a day as required.	Unchanged
Tramadol 50 mg	Take ONE capsule daily when required for migraines.	Unchanged
Rizatriptan 10 mg	Use ONE wafer on the tongue daily when required.	Unchanged
Ranitidine 150 mg	Take ONE tablet twice a day when required.	Unchanged
Salbutamol 100 µg	Inhale TWO doses four times a day as required.	Unchanged

Note: Patient was taking candesartan prior to sacubitril/valsartan; sacubitril/valsartan commenced in May 2019.

Clinic 28 January 2020—Medication list (cessation of sacubitril/valsartan)

Candesartan 8 mg	Take ONE tablet in the twice a day.	New
Nebivolol 5 mg	Take ONE tablet at night.	Unchanged
Frusemide (furosemide) 40 mg	Take HALF a tablet in the morning as required.	Unchanged
Magnesium	Take ONE tablet in the morning.	Unchanged
Coenzyme Q10	Take ONE capsule in the morning.	Unchanged
Insulin aspartate mix30	Inject when blood sugar level is >12, administer TEN units daily when required. Give with food.	Unchanged
Paracetamol 500 mg	Take TWO tablets four times a day as required.	Unchanged

Continued

Table I *Continued*

Tramadol 50 mg	Take ONE capsule daily when required for migraines	Unchanged
Ranitidine 150 mg	Take ONE tablet twice a day when required.	Unchanged
Beclomethasone 100 µg	Inhale ONE dose twice a day.	Unchanged
Salbutamol 100 µg	Inhale TWO doses four times a day as required.	Unchanged
Loratadine 10 mg	Take ONE tablet daily as required.	Unchanged
Sacubitril-valsartan 24 mg/26 mg	Take ONE tablet twice a day.	Ceased—changed to candesartan

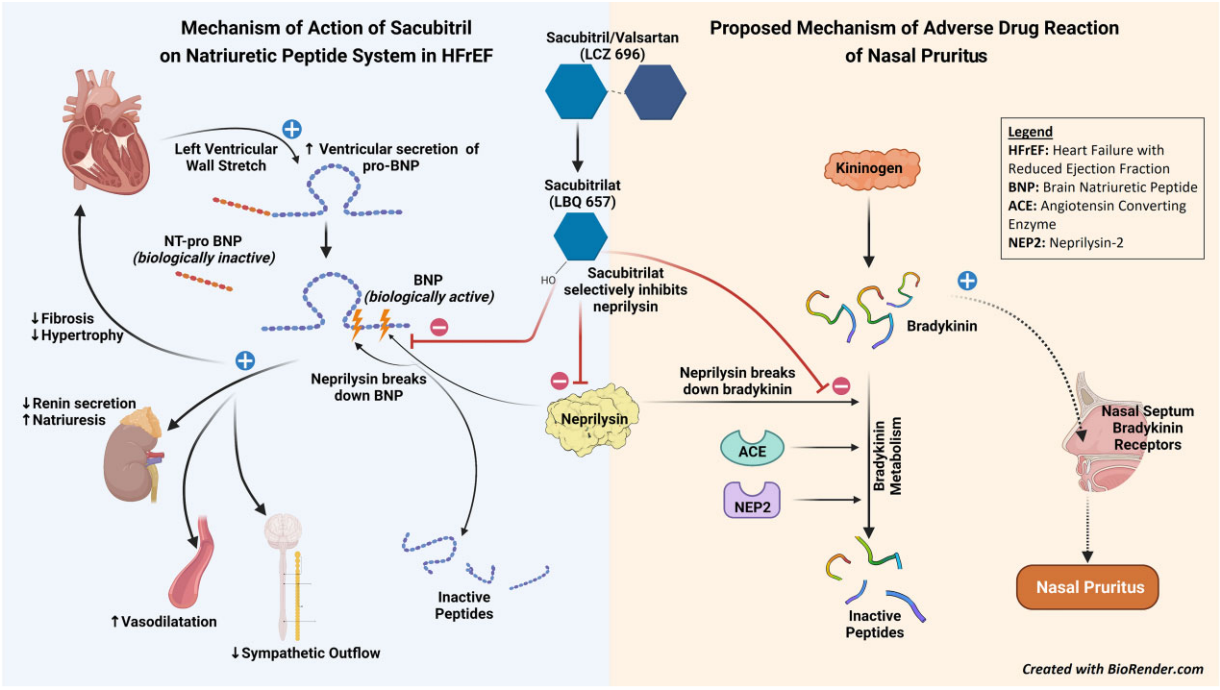


Figure 1 Mechanism of action of sacubitril and proposed mechanism of nasal pruritus.

The patient reported constant nasal pruritus started three days after taking sacubitril/valsartan 24/26 mg twice daily, solely at the nasal septal area. Self-initiated daily use of anti-histamine medication was used to suppress the itch with no alleviation over 8 months. During this time, the dose was up-titrated to 49/51 mg twice daily, and then down-titrated to 24/26 mg twice daily (due to orthostatic hypotension), but the nasal itch remained constant. The sacubitril/valsartan 24/26 mg twice daily was ceased (as an initial trial) and was switched to candesartan, resulting in complete alleviation of the nasal pruritus.

Discussion

The clinical presentation of nasal pruritus post-initiation of sacubitril/valsartan is consistent between the three case reports. These cases were reported to the Australian pharmacovigilance authority (Therapeutic Goods Administration). All individuals described similar constant pruritus at the nasal septum; the same location for all three cases (*Figure 2*). Despite the use of anti-histamines, the pruritus did not subside. Interestingly, the severity of pruritus was not dose-dependent as a trial of down-titrating the sacubitril/valsartan dose did not alleviate the pruritus. As a result, all individuals discontinued sacubitril/valsartan within 3–8 months, with complete resolution of their nasal pruritus. Who 'nose', it may be the sacubitril/valsartan.

Several studies have highlighted a decline in the quality of life in patients suffering from symptoms of allergic rhinitis; it has been associated with increased risk of depression, behavioural and emotional disorders.[4–7] The constant nasal pruritus experienced by our patients had been so severe that they had decided to discontinue sacubitril/valsartan. Upon cessation, there was a complete alleviation of nasal

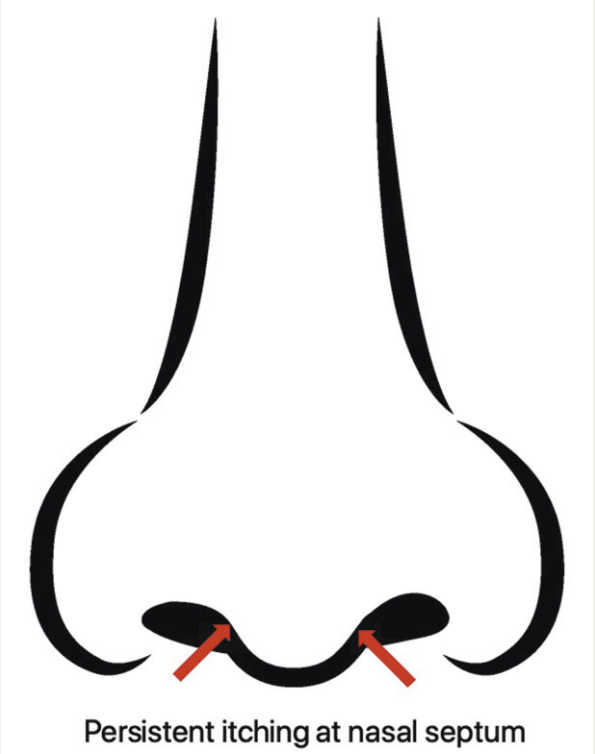


Figure 2 Reported site of nasal pruritus—same location for all three patients.

pruritus. All three patients in our series have declined to recommence of sacubitril/valsartan despite experiencing symptomatic and objective echocardiographic improvement of their underlying HFrEF.

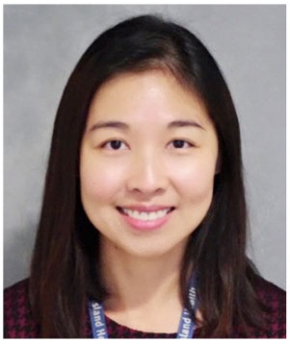
Several chemical mediators, such as histamine, bradykinin, cysteinyl leukotrienes, platelet-activating factor, prostaglandin D_2, and thromboxane A_2 are involved in the complex process of nasal allergic response.[8,9] Little is known about sacubitril causing nasal irritation. Most literature discussed ACE inhibition causing bronchial mucosa irritation were explained by bradykinin accumulation.[8,10] Other mechanisms potentiating this inflammatory reaction include histamine release from mast cells due to bradykinin, substance P, leukotrienes, and prostaglandins.[10,11] Among patients with allergic airways, up-regulation of histamine H_1 receptor in epithelial and vascular endothelial cells were shown in immunohistochemical studies.[8] Combination of both sacubitril and valsartan may up-regulate the complex inter-play of chemical mediators and receptors in a susceptible individual. However, the administration of anti-histamine had not alleviated the symptom in our patients. We attempted to perform a retrospective review to check for shifts in blood counts (in particular eosinophils) and other inflammatory markers. As these tests were not routinely ordered in our heart failure titration clinic, only one case (Case 3) had a baseline full blood count recorded and there was no shift in the patient's eosinophils during sacubitril/valsartan exposure. Of note, we have yet to evaluate the effect of intra-nasal corticosteroids among these patients.

Interestingly, all the described cases in this series did not report significant nasal congestion and rhinorrhea. We hypothesize that based on this observational divergence as compared to allergic rhinitis, the mediator(s) in ARNi-mediated nasal pruritus may not involve similar extend of mast cells degranulation and histamine releases as observed in seasonal and perennial allergic rhinitis. The symptoms of nasal pruritus may potentially be mediated by increased local bradykinin along the nasal septum, rather than a true hypersensitivity response as in allergic rhinitis (*Figure 1*). Nevertheless, unless immunohistochemical analyses were performed to determine the expression and distribution of these receptors in susceptible individual, we were unable to conclude which chemical mediators are driving the nasal pruritus.

Conclusion

Based on the known pharmacological effect of sacubitril on bradykinin, the described cases of persistent but reversible nasal pruritus coinciding with the commencement of ARNi raises the possibility of this less-known adverse drug reaction. Although the effect of nasal symptoms is far less prognostically significant compared to the adverse outcomes associated with HFrEF, the constant nasal pruritus and the associated impact on the quality of life and mood disturbance may prompt patient's desire to discontinue ARNi permanently.

Lead author biography



Jaclyn Gan is a clinical pharmacist who has been practicing in hospital setting for the last 20 years, after completing her Bachelor of Pharmacy at the University of Queensland in 2001. In 2007, she joined The Prince Charles Hospital, a 600-bed tertiary referral hospital in Brisbane, Australia, specializing in cardiology. Areas that she has worked in, include heart transplant, heart failure, adult congenital heart disease, and general cardiology. She was the co-founder of the first interdisciplinary nurse practitioner and pharmacist clinic in Queensland. She is currently a pharmacy team leader in cardiology and is also a co-chair of the statewide heart failure pharmacy network.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

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