

LETTER TO THE EDITOR

Raynaud's phenomenon triggered by the vasopressin V₂ receptor antagonist tolvaptan in a patient with autosomal dominant polycystic kidney disease and Sjögren's syndrome

F. J. Roca Oporto  and Jose L. Rocha

Hospital Universitario Virgen del Rocio, Nephrology, Sevilla, Spain

Correspondence to: Francisco Roca Oporto; E-mail: fcoj.roca.sspa@juntadeandalucia.es

Autosomal dominant polycystic kidney disease (ADPKD) is the most widespread monogenic kidney disease, accounting for 5–10% of all end-stage kidney disease cases among adults. Tolvaptan, a highly selective non-peptide arginine vasopressin V₂ receptor antagonist, down-regulates the total kidney volume overload and delays kidney function decline in patients with ADPKD [1]. The European Medicines Agency has approved the use of tolvaptan to delay the progression of cyst development and renal insufficiency in adult patients with ADPKD associated with chronic kidney disease (CKD) stages 1–3 while initiating treatment for cases with evidently rapid disease progression. The ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice have proposed a hierarchical decision algorithm to accurately identify rapid disease progression [2].

A 34-year-old woman with stage 2 CKD due to ADPKD also had an oligosymptomatic primary Sjögren's syndrome with Raynaud's phenomenon, without evidence of active disease and an absence of attacks for 10 years. She was receiving irbesartan for mild arterial hypertension and no specific treatment for Raynaud's phenomenon or Sjögren's syndrome other than nonpharmacologic measures.

She fulfilled the criteria to initiate tolvaptan treatment with an average annual estimated glomerular filtration rate decline of 10 to 5 mL/min/1.73 m² over 5 years. Tolvaptan (60 mg/day) was started under informed consent in November 2017. No other changes in medication were made.

Five days after initiating tolvaptan she developed a heavy Raynaud's episode affecting both hands and feet, with clearly

demarcated color changes of the skin (Figure 1) that improved when placed in warm water. Raynaud's phenomenon episodes were frequent and intense for a few weeks. The symptoms improved with general measures and were well tolerated. Tolvaptan therapy was maintained with close monitoring.

The most frequent adverse events related to tolvaptan treatment are thirst, polyuria, hyperuricemia and hepatic events [3]. To the best of our knowledge, this is the first description of Raynaud's phenomenon related to tolvaptan therapy.

Arginine vasopressin plays a vital role in water and circulatory homeostasis through activation of three receptor subtypes (V1a, V1b and V2) that have different effects and sites of expression [4]. V1a receptors primarily exist in vascular smooth muscle and promote vasoconstriction and cardiac hypertrophy. V1b receptors are scattered widely and their activation is part of the adaptive reaction to stress, causing the release of adrenocorticotropic hormone and endorphin. V2 receptors are predominantly expressed in principal cells of the renal collecting duct system and increase free water resorption. V2 receptors are also found in pneumocytes type 2, vascular endothelium releasing von Willebrand factor and factor VIII and vascular smooth muscle. V2 activation causes vasodilatation, as opposed to V1a receptors that exert a vasoconstrictive effect. A V₂ receptor antagonist like tolvaptan may block the vasodilatory effect and cause clinical symptoms, which are more pronounced among predisposed patients, such as our patient with pre-existing Raynaud's phenomenon. Interestingly, a potent, selective V1a-receptor antagonist, relcovaptan, has shown positive results in treating Raynaud's phenomenon.

Received: 20.11.2021; Editorial decision: 6.12.2021

© The Author(s) 2021. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com



FIGURE 1: Symptoms of Raynaud's phenomenon with demarcated colour changes of the skin (blue arrow).

Vasopressin V2 receptor antagonists are a new class of drugs indicated in hyponatremia, heart failure, liver cirrhosis and, more recently, ADPKD. Severe adverse events for these drugs are rare. However, their long-term effects have not been extensively studied and their widespread use might reveal unknown adverse events.

Given the physiological effects of V2 subtype receptors other than water resorption, predisposed patients may experience vasoconstrictive effects on smooth muscle with clinical outcomes.

DATA AVAILABILITY STATEMENT

Data available on request.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PATIENT CONSENT

Informed consent was obtained for the publication of this case report and accompanying images.

REFERENCES

1. Torres VE, Chapman AB, Devuyst O *et al*. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–2418
2. Gansevoort RT, Arici M, Benzing T *et al*. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA–EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrol Dial Transplant* 2016; 31: 337–348
3. Blair HA. Tolvaptan: a review in autosomal dominant polycystic kidney disease. *Drugs* 2019; 79: 303–313
4. Decaux G, Soupart A, Vassart G. Non-peptide arginine-vasopressin antagonists: the vaptans. *Lancet* 2008; 371: 1624–1632