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Javier Deira[a,*], Cristina García de la Vega[a], Elena Davín[a], María José Arcos[b]

[a] *Servicio de Nefrología, Hospital San Pedro de Alcántara, Cáceres, Spain*
[b] *Servicio de Hematología, Hospital San Pedro de Alcántara, Cáceres, Spain*

[*] *Corresponding author.*
E-mail address: javierlorenzo.deira@salud-juntaex.es (J. Deira).

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Hepatotoxicity induced by tolvaptan: A case report

Hepatitis tóxica inducida por tolvaptan: a propósito de un caso

ARTICLE INFO

Dear Editor,

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent hereditary kidney disease. Its estimated prevalence is highly debated and ranges from 1 in every 500 to 1 in every 2000 people.[1–4] Patients with ADPKD represent between 6% and 10% of the population on dialysis or kidney transplant, meaning that it is a disease with a major social impact.[5]

In 2015, the use of tolvaptan was approved in Europe for the treatment of patients over the age of 18 years with ADPKD and CKD stage 1-3 at the initiation of treatment and with signs of rapid progression in order to slow down the course of the disease.

The most frequent side effects of tolvaptan are aquaretic side effects (between 65%–95% of the patients have them).[6] For this reason, patients must have continuous access to water and maintain an adequate water intake in accordance with their diuresis.

However, the side effect requiring the greatest attention is idiosyncratic hepatotoxicity. In order to maintain a control this negative effect, liver function tests (LFT) must be monitored every month during the first 18 months of treatment and every three months thereafter as indicated by the autosomal dominant polycystic kidney disease consensus document published in 2020.[7]

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In the *Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes* (TEMPO) 3:4 study, the incidence of liver damage defined as an elevation of alanine aminotransferase (ALT) three times the upper limit of normal was 4.4%,[8] and we did not find liver damage indices as high as those of our own centre in the literature.[9,10]

In our experience, the incidence of liver toxicity is higher, since six of the 17 patients who received tolvaptan at our centre had altered LFT and the drug had to be definitively discontinued in two of them. Mean ALT was 192 U/L (54–544 U/L). These data increase the incidence to 35% in our series.

We present the case of one of the patients who required the discontinuation of the drug due to liver toxicity.

The patient is a 45-year-old man diagnosed with ADPKD in 2002 after an abdominal ultrasound. As complications of the disease, he presented recurrent urinary infections and was hypertensive and on treatment with olmesartan. In accordance with rapid progression criteria (Mayo Clinic 1D classification), treatment was initiated in March 2018 and liver function was monitored monthly. The dose of tolvaptan was 45 + 15 mg the first month, 60 + 30 mg the second month and reached the maximum dose (90 + 30 mg) in June 2018.

In the control of LFT in July 2018, it was observed an increase in ALT, with values of 211 U/L (4–41 U/L normal value), whereupon the dose was down-titrated to the inter-

mediate dose. However, biochemical alterations persisted and the treatment was ultimately suspended.

Two weeks later, a new analytical control was performed, showing a considerable increase in liver enzymes, with ALT values of 544 U/L, whereby in view of the severity of the symptoms despite the suspension of the treatment with tolvaptan, an evaluation by GI specialist was requested.

The complementary studies were expanded, liver virus and autoimmunity serologies were performed, as well as an urgent abdominal ultrasound, and acute liver disease was ruled out.

LFT did not revert to normal until three months after the suspension of the drug, and a diagnosis of toxic hepatitis secondary to tolvaptan treatment was made.

In conclusion, idiosyncratic hepatotoxicity associated with treatment with tolvaptan may be a more common phenomenon in clinical practice than the literature would suggest. For this reason, we believe that LFT should be monitored exhaustively and monthly over the first 18 months of treatment, as explained in the consensus document on autosomal dominant polycystic kidney disease.[7]

In our experience, LFT values have always reverted to normal following suspension of the drug, although in cases of severe toxicity it may take up to three months to resolve.

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Maria del Carmen Merino Bueno[a,*], Cristina Sango Merino[a], Anna Gallardo Pérez[a], Susana Rojo Alba[b], Carlos Ruiz Zorrilla[a], Miguel Angel de la Torre Fernández[a], Ana Maria Suárez Laures[a], Emilio Sánchez Álvarez[a]

[a] *Servicio de Nefrología, Hospital Universitario de Cabueñes, Gijón, Asturias, Spain*
[b] *Servicio de Microbiología, Hospital Universitario Central de Asturias, Oviedo, Spain*

* Corresponding author.
E-mail address: carmenmbueno@gmail.com (M.d.C. Merino Bueno).

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