Reply to letter to editor comment on "Cellular and molecular aspects of diabetic nephropathy; the role of VEGF-A"☆

Respuesta a la carta al editor referida a «Mecanismos celulares y moleculares de la nefropatía diabética, rol del VEGF-A»

Dear Editor,

We appreciate the valuable comments of the authors of the letter to the editor. They allude to the renal side effects (RSE) of anti-VEGF-A antibodies (anti-VEGF-A) administered intravitreally. They also share the story of a patient with diabetic retinopathy (DR) who developed nephrotic syndrome (NS) 10 days after receiving intravitreal anti-VEGF-A. From a multidisciplinary perspective, comments remind nephrologists of the need to treat the different RSE caused by commonly used agents more frequently.

The clinical case suggests several differential diagnoses: Will this be *de novo* glomerulopathy? Was NS caused by glomerulopathy added to a preexisting diabetic nephropathy (DN)? Did the anti-VEGF-A trigger the DN? A renal biopsy (optical/electronic microscopy) is essential for diagnosing kidney disease and for indicating the specific treatment. In this patient, decreased glomerular/systemic VEGF-A could have mainly affected the podocytes and glomerular basement membrane. If the glomerular endothelium was also affected, the patient could be suffering from thrombotic microangiopathy (TMA), a complication similar to preeclampsia. Notably, important histological alterations of TMA accompanied by relatively minor biological signs useful for clinical diagnosis were described. In addition, Up to 50% of the patients presented exclusively localized MAT to the kidney.[1–3] Regarding treatment, is indicated in this patient to suspend the anti-VEGF-A agents due to NS. Treatment of anti-VEGF-A-induced kidney disease will depend on the anatomical pathology of kidneys.

Although anti-VEGF-A have been used for more than a decade to treat cancer, their RSE have been underestimated and their exact frequency is unknown.[1] The most frequently reported anti-VEGF-A-related RSE include: incidence of hypertension (HTN; 20–42%) and incidence of proteinuria (20–62%).[2] Other lesser-described RSE include: TMA; NS; focal segmental glomerulosclerosis (FSGS); collapsing FSGS; immunoglobulin-A glomerulopathy; pauci-immune extracapillary glomerulonephritis; membranoproliferative glomerulonephritis; minimal change disease (MCD); acute and chronic kidney failure; interstitial nephritis; vascular alterations and hydroelectrolytic disorders.[1–3] The RSE increased in a dose-dependent manner and when combined with chemotherapy.[1–3] The risk of RSE was higher in elderly patients with multiple complications, high cardiovascular risk, diabetes mellitus (DM) and high doses/cycles of anti-VEGF-A.[2]

The frequency of RSE after intravitreal administration of anti-VEGF-A was less defined, although they appear to be smaller.[4–8] HTN and proteinuria were described in 0.2% and 0.6% of the cases, respectively.[4] Some individual clinical cases reported membranous glomerulonephritis (MGN),[5] recurrence of MCD[6] and severe impairment of renal function in people with preexisting DN.[7] In transplanted kidneys, there was a deterioration of glomerular filtration (GF) and proteinuria related to MGN, changes compatible with acute and chronic rejection, glomerular thrombi and transplant glomerulopathy.[8]

Agents that decrease concentration and inhibit the activity and signaling cascade of VEGF-A at a glomerular level can induce serious renal impairment.[1–3,9,10] The first anti-VEGF-A used to treat cancer was bevacizumab. This antibody was also globally prescribed by ophthalmologists.[1–4] Bevacizumab is a recombinant monoclonal antibody that binds to all VEGF-A isoforms. Its intravitreal administration greatly reduces vitreous VEGF-A, including levels previously increased by DM.[10] Bevacizumab has a propitious size to stay at the injection site, (149 kDa), but it can reach the systemic circulation rapidly, thus maintaining a prolonged half-life.[9] Although intravitreal doses of bevacizumab (1–2.5 mg) are lower than the doses used systemically to treat eye disorders (5 mg/kg) and cancer (5–15 mg/kg), levels of free-circulating VEGF-A decreased after 24 h up to 4 weeks after intravitreal administration.[1–4,9,10] In patients with DR, serum levels of VEGF-A decreased one day after receiving intravitreal bevacizumab, but the maximum reduction occurring on day seven.[10] Moreover, in patients with age-related macular degeneration, intravitreal bevacizumab passed rapidly into the bloodstream and remained in circulation, causing a marked decrease in plasma VEGF-A.[9] Plasma VEGF-A decreased one week after the first dose, remaining lower than baseline and further decreasing one week after the third dose.[9] In the patient described in the letter to the editor, systemic and glomerular VEGF-A may have decreased markedly at the onset of NS, and so defining the risk ranges would be relevant.

In summary, conducting clinical trials to determine anti-VEGF-A-induced RSE is a pending task. Quantifying GFR and

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microalbuminuria/proteinuria before and during treatment with anti-VEGF-A could help to detect RSE early. In view of the diagnosis of severe RSE, we consider performing a renal biopsy to be key in early detection. Quantifying GFR, microalbuminuria/proteinuria and plasma VEGF-A before and after each cycle/injection of anti-VEGF-A would provide useful data for the prevention, diagnosis and treatment of RSE. Moreover, free-circulating VEGF-A could be used as an early biomarker of RSE secondary to treatment with anti-VEGF-A.

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Reaction to synthetic membranes in hemodialysis☆

Reacción a membranas sintéticas en hemodiálisis

Dear Editor,

Although the incidence of hypersensitivity reactions in haemodialysis (HD) is low and their severity varies, these reactions are not rare and can be lethal.[1] Recently several cases associated with the use of synthetic membranes have been reported.[2] These reactions are either mild to moderate, with minimal clinical repercussions that go unnoticed, or severe with a wide range of symptoms which could prove lethal.[1,2]

We report the case of an 80-year-old man with chronic kidney disease of vascular aetiology, receiving treatment with HD since January 2016.

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