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Renal damage associated to intravitreal administration of ranibizumab☆

Daño renal asociado a la administración intravítrea de ranibizumab

Dear Editor,

Vascular endothelial growth factor (VEGF) promotes angiogenesis and is being produce by several types of tumors. The production of VEGF by tumors is related to aggressiveness, growth and their capabilities to produce metastasis and relapse. Inhibitors of angiogenesis (anti-VEGF) are effective therapeutic options for the treatment of patients with metastatic tumors. They are generally well-tolerated drugs, but the increase in use has shown secondary effects including at the renal level.[1,2]

Recently, the intravitreal use of this type of antiangiogenic therapies has been a revolution in the field of Ophthalmology.[3,4] Age-related macular degeneration, diabetic macular edema, or macular edema secondary to retinal vein occlusion are some of the entities that have been most frequently benefited from the use of anti-VEGF. However, there is little information on the renal adverse effects of these drugs when administered intraocularly.

We describe the case of a patient with chronic kidney disease secondary to diabetic nephropathy who presented impaired renal function and increased proteinuria following the administration of several doses of ranibizumab for the treatment of diabetic retinopathy.

The patient is 56-year-old male, obese, smoker, and diagnosed of type 2 diabetes mellitus with good glycemic control (glycated hemoglobin ≤7% total Hb) on insulin therapy. The patient had severe proliferative diabetic retinopathy with significant decrease in visual acuity and chronic renal failure secondary to biopsy proven diabetic nephropathy (Class IV diabetic glomerulosclerosis). During his follow-up in the Nephrology clinic, in spite of the advanced of his renal insufficiency, he was able to stabilize the progression of his renal disease (serum creatinine 2.6 mg/dl and proteinuria 2.6 g/24 h) with the use of systemic-renin-angiotensin-aldosterone blockers, good blood pressure control and excellent glycemic control (glycated hemoglobin 6.3%). However, in one of the clinic visits, the patient had an acute deterioration of renal function (serum creatinine 4.1 mg/dl) with a significant increase in the amount of proteinuria (proteinuria 9.4 μg/24 h) without changes in their usual medication and with good control of their blood glucose. The only change was the intravitreal administration of ranibizumab as a treatment for diabetic retinopathy. Renal function has continued to deteriorate and renal replacement therapy is pending.

The question to be addressed is whether the intravitreal administration of anti-VEGF drugs may produce renal adverse effects similar to those seen with systemic administration. It is known that the systemic administration of this type of drugs may produce hypertension, proteinuria and thrombotic microangiopathy as secondary renal adverse effects.[1,2] Treatment of vitreoretinal neovascular disease has undergone some vertiginous changes over the last 2 decades, from the classic treatments to the use of new drugs that block VEGF such as ranibizumab, bevacizumab and pegaptanib. Among the most common adverse effects associated with this type of therapy are local ocular reactions and, less frequently, systemic processes such as pulmonary thromboembolism or hypertension.[5] However, there is little information on renal

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Table 1 – Patients reported in the literature with renal involvement after intravitreal administration of anti-VEGF drugs.

Ref	Age/gender	Medical history	Clinical presentation	Eye disease	Medication	Outcome
3		Diabetes mellitus (3 patients)	Reduction of renal function	Proliferative diabetic rethinopathy	Bevacizumab	
6	77/F	Hypertension (sCr 0.99 mg/dl)	TMA (renal biopsy)	Macular degeneration	Ranibizumab	Recovery of Renal Function
7		Diabetes mellitus (1 patient)	Reduction of renal function	Proliferative diabetic rethinopathy		
8	16/F	Minimal change	Relapse of nephrotic syndrome	Coroidal neovascularization Secondary to myopia	Bevacizumab	Full remission
9	68/F 59/M	Diabetic nephropathy (GFR: 21 ml/min) Diabetic nephropathy (GFR: 25 ml/min)	Increase in proteinuria Reduction of renal function	Proliferative Diabetic retinopathy Proliferative diabetic retinopathy	Ranibizumab Bevacizumab	Hemodialysis Hemodialysis
10	67/M 52/M	Renal transplant (sCr 1.7 mg/dl) Renal transplant (Crs 2.8 mg/dl)	Increase of proteinuria MGN (renal biopsy) Increase of proteinuria Renal function deterioration	Macular degeneration Macular Degeneration	Bevacizumab Ranibizumab	

Crs: serum creatinine; GFR: glomerular filtration rate; MGN: membranous glomerulonephritis; F: female; TMA: thrombotic microangiopathy; M: male.

adverse effects from the intravitreal administration of these anti-VEFG4 monoclonal antibodies. One possible explanation could be the minimal dose used in ophthalmology (400 times less) and the ocular barrier involves a local drug sequestration and a delay in its systemic absorption. However, we must not forget that, although it is a local administration, this retinal blood barrier is altered due to the ongoing ophthalmological processes and that the elimination of these antiangiogenic agents is systemic. Renal involvement by intravitreal administration of antiangiogenic drugs is reflected in several clinical cases reported during the last years [6–10] (Table 1). Pelle et al. reported the case of a hypertensive patient with normal renal function who developed acute renal failure with thrombotic microangiopathy after the administration of ranibizumab for the treatment of macular degeneration.[6] The consequences may be more significant, such as the cases of diabetic patients with advanced chronic kidney disease who required dialysis after administration of an anti-VEFG.[9] These renal adverse effects have also reached the world of renal transplantation; recently, it has been reported that 2 patients developed impaired renal function and increased proteinuria after intravitreal administration of an anti-VEFG.[10]

In conclusion, due to the widespread use of this type of drugs in a patient population such as diabetes may demand, strict follow-up protocols by ophthalmologists and nephrologists (blood pressure measurement, determination of proteinuria and serum creatinine) before and after of the administration of the antiangiogenicos. These measures will help to establish an early diagnosis of the possible renal complications.

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Immediate re-transplantation: An audacious approach to early vascular renal transplant failure☆

Trasplante exprés: un tratamiento audaz en el fallo técnico precoz del injerto

Dear Editor,

Renal transplantation is the treatment of choice in patients with advanced chronic kidney disease (CKD) as it improves the quality of life and survival of patients.[1]

Vascular complications of renal transplantation represent an important cause of morbidity and mortality, and frequently lead to early graft loss,[2] which is around 5% in the most recent series.[3] A 4–10% of patients who start dialysis have a non-functioning kidney graft, and up to 32% of cases require transplantectomy for various reasons.[4] The mortality of these patients is greater than those with functional graft or in renal replacement therapy without previous transplantation.[5] Current indications for transplantectomy include early graft loss, intolerance syndrome, severe proteinuria, recurrent pyelonephritis, neoplasia, and chronic inflammation syndrome.[6] Early vascular complications of transplantation may cause the loss of the graft and the need for transplantectomy.

The performance of express transplant seeks to obtain the benefit of performing an inevitable transplantectomy with the implantation of another graft in the same surgical act. This improves both quality of life and survival of the patient,[5] in addition to ameliorating the psychological problem of early graft loss.

In patients with terminal liver disease, re-transplantation after early graft loss is common otherwise the prognosis is very poor.[7] In renal transplantation, such a degree of urgency does not exist due to the availability of other renal replacement techniques,[1] thus re-transplantation is not performed early.

The term express used here as the definition made by the Royal Spanish Language Academy "with maximum speed".[8]

We have performed a total of 4 express transplants over a period of 2 years, describing their characteristics and evolution in Table 1.

The immediate loss of the graft is included among the indications of transplantectomy and, in this case, it must be performed rapidly, since this almost immediate intervention can prevent foreseeable complications such as graft intolerance, rupture of the graft, infections and formation of antibodies ensuing hyperimmunization of the patient.[6,9]

Performance of express transplant has several advantages: it avoids the morbimortality of the transplantectomy as a necessary but isolated act, since in the same act another transplant is carried out, immunosuppression is maintained which prevents the formation of antibodies and the hyperimmunization of the patient and finally it avoids the negative psychological impact of graft loss and preserves the confidence of patient on the actual medical care.

Prior to the procedure, it is important to rule out other causes of early graft loss, such as hyperacute rejection,[10] or problems with hypercoagulability[9] since both situations would contraindicate express transplantation. In our cases, the immunological study carried out after graft loss, the histological absence of acute rejection and the lack of history of

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