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From the Clinic

Raloxifene and Bevacizumab for severe complications of hereditary haemorrhagic telangiectasia in a haemodialysis patient

Hereditary haemorrhagic telangiectasia (HHT), or Osler–Weber–Rendu syndrome, is inherited in an autosomal-dominant fashion. There are two different forms of HHT: HHT type 1, caused by mutations in the endoglin gene, located in chromosome 9 (which encodes endoglin), and HHT type 2, caused by mutations in the gene encoding activin A receptor type II-like 1 (ALK1) on chromosome 12. Mucocutaneous telangiectasias, arteriovenous malformations, epistaxis, gastrointestinal bleeding and iron-deficiency anaemia are the commonest clinical manifestations of HHT [1]. Hepatic involvement, characterized by different arteriovenous malformations within the liver parenchyma, occurs in up to 74% of patients with HHT [2]. As far as we know, no information has been published on therapeutic alternatives for haemodialysis patients suffering from severe complications of HHT.

We report on a 59-year-old woman with chronic renal failure secondary to bilateral renal hypoplasia and undergoing haemodialysis, who received the diagnosis of HHT. She had presented relapsing epistaxis during the last year, with severe anaemia and hypotension. Due to the need for weekly transfusions and the poor tolerance to haemodialysis sessions, we consider treatment with raloxifene (60 mg/day), a selective estradiol receptor modulator. Raloxifene increases the expression of endoglin and ALK1, whose synthesis is defective in HHT patients, at the surface of endothelial cells [3]. A remarkable improvement of HHT symptoms along with a significant decrease in the number and severity of epistaxis was observed after raloxifene treatment. However, 6 months after the onset of raloxifene treatment, the patient presented with signs and symptoms of high-output cardiac failure, with severe ascites and a left pleural effusion. Increase of haemodialysis ultrafiltration along with large-volume paracentesis were started, but the patient showed a poor tolerance to these measures, owing to the presence of anaemia, hypotension and chronic liver disease. Serum biochemistry demonstrated a progressive cholestasis. A computed tomography (CT) scan showed liver cirrhosis with splenomegaly and massive arteriovenous malformations (Figure 1). Prompted by the progressive clinical deterioration of the patient, we decided to start treatment with bevacizumab, a humanized recombinant monoclonal antibody against the vascular endothelial growth factor (VEFG). The VEGF is a key regulator of angiogenesis and is upregulated in a variety of diseases. On the other hand, endoglin and ALK1 are involved in the transforming growth factor-β signalling pathway, which is a potent stimulator of VEFG production. Bevacizumab has been shown to be effective in diseases of abnormal angiogenesis, improving survival and symptomatology [4, 5]. Bevacizumab has been also used for the treatment of liver complications of HHT, inducing a clear improvement [6]. After obtaining the patient's informed consent, six courses of bevacizumab (5 mg/kg) were administered during a 3-month period and raloxifene was maintained without changes. A further reduction in the frequency of epistaxis was observed besides a remarkable improvement of ascites and liver enzymes. As shown in Figure 1, serial CT scans demonstrated a clear diminution of hepatic vascularity and a smooth contour of the liver.

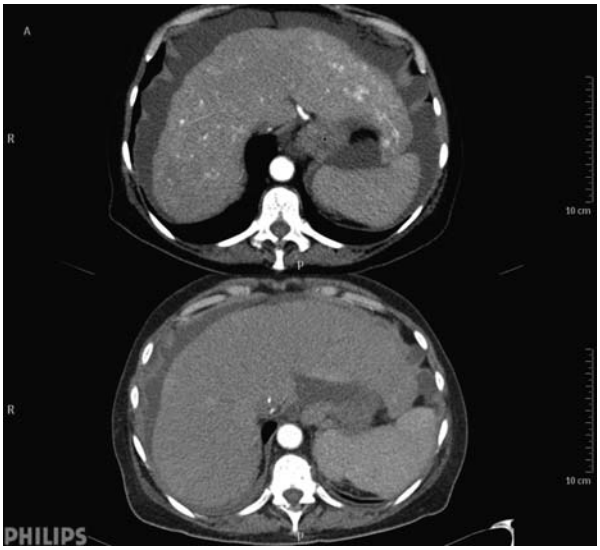

Fig. 1. CT scan of the liver with intravenous contrast before and 6 months after bevacizumab treatment, showing a dramatic reduction of vascularity and improvement of liver surface.

Many different therapies have been proposed for epistaxis and hepatic involvement in HHT, but none of them have shown conclusive results. Hormonal therapy with estradiol for epistaxis and gastrointestinal management of HHT has shown a variable degree of efficacy depending on the patient. According to our experience, both raloxifene and bevacizumab are very effective alternatives for the treatment of severe HHT in haemodialysis patients.

Conflict of interest statement. None declared.

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References

1. Fuchizaki U, Miyamori H, Kitagawa S *et al*. Hereditary hemorrhagic teleangiectasia (Rendu–Osler–Weber disease). *Lancet* 2003; 362: 1490–1494
2. Bernabéu C, Blanco FJ, Langa C *et al*. Involvement of the TGF-B superfamily signalling pathway in hereditary haemorragic teleangiectasia. *J Appl Biomed* 2010; 8: 169–177

3. Dupuis-Girod S, Chesnais AL, Ginon I *et al*. Long-term outcome of patients with hereditary hemorrhagic teleangiectasia and severe hepatic involvement after orthotopic liver transplantation: a single center study. *Liver Transpl* 2010; 16: 340–347
4. Albiñana V, Bernabeu-Herrero ME, Zarrabeitia R *et al*. Estrogen therapy for hereditary hemorrhagic teleangiectasia (HHT): effects of raloxifene, on endoglin and ALK1 expression in endothelial cells. *Thromb Haemost* 2010; 103: 525–534
5. Bose P, Holter JL, Selby GB. Bevacizumab in hereditary hemorrhagic teleangiectasia. *N Engl J Med* 2009; 360: 2143–2144
6. Mitchell A, Adams LA, MacQuillan G *et al*. Bevacizumab reverses need for liver transplantation in hereditary hemorrhagic teleangiectasia. *Liver Transpl* 2008; 14: 210–213

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