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LETTERS

Hereditary haemorrhagic telangiectasia: From symptomatic management to pathogenesis based treatment

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I read with interest the article 'Hereditary haemorrhagic telangiectasia: a clinical and scientific review' by Govani and Shovlin.[1] As the authors show in Table 2, treatment of patients with hereditary haemorrhagic telangiectasia (HHT), currently, is primarily symptomatic, without alteration of the underlying pathological process. HHT is a disorder of unbalanced angiogenesis. The vascular endothelial growth factor (VEGF) is upregulated in patients with HHT,[2] and this factor induces angiogenesis by stimulation of endothelial cell proliferation and migration. Likewise, it stimulates expression of matrix metalloproteinases, which are needed for the degradation of the extracellular matrix in the angiogenic process. In recent years, antiangiogenic drugs have been incorporated into the treatment of HHT. Owing to the important role of VEGF in HHT, drugs against this factor, such as bevacizumab, have been used with favourable outcome in this process.[3–5] Lenalidomide, a derivative of thalidomide, proved to be useful in a patient with chronic gastrointestinal bleeding as well as sudden massive life-threatening bleeds.[6] These clinical observations opened the door to the investigation of pathogenesis-based treatment. From a theoretical standpoint, it might be of interest to evaluate other drugs with fewer side effects.[7] For example, doxycycline is considered to inhibit angiogenesis through the inhibition of matrix metalloproteinases, and matrix metalloproteinases are increased in some patients with HTT.[8] This antibiotic appeared to be beneficial in other disorders with unbalanced angiogenesis[9] or increased activity of matrix metalloproteinases.[10] Against this background, I believe that it might be of interest to investigate whether doxycycline might have a role in the treatment of some patients with HHT.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Reply to Fernández-Fernández

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Dr Fernandez-Fernandez[1] is right in raising the important new data regarding anti-angiogenic strategies in hereditary haemorrhagic telangiectasia (HHT), data which were published too late for inclusion in our review.[2] Although the gene mutations inform us that HHT is a disorder caused by aberrant signalling by the transforming growth factor (TGF)-β superfamily, the context in which the gene mutations are deleterious, when functioning apparently perfectly well for the vast majority of vessels, has always proved tantalising. In 2009, there has been a resurgent interest in the role of angiogenesis in provoking or unmasking an HHT phenotype, with animal models particularly implicating a role for aberrant angiogenesis during wound healing.[3] Pathogenesis-based treatment strategies based on case reports using anti-VEGF (bevacizumab/Avastin),[4–6] interferon,[7,8] and thalidomide[9,10] are being assessed in ongoing clinical trials at HHT centres. For any efficacious agent, side-effect profiles are likely to be crucial in determining whether the use of any efficacious agents can become more widespread within the HHT patient population. In 2009, encouraging data were also reported for two better-tolerated agents, *N*-acetyl cysteine (trial data for 600 mg tds)[11] and tamoxifen (randomised placebo-control trial data for 20 mg/day).[12] These have been introduced into specialised HHT practice, reflecting the rapidly advancing field.

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Hereditary haemorrhagic telangiectasia and genetic thrombophilia

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Govani and Shovlin[1] recently described the clinical and diagnostic implications of hereditary haemorrhagic telangiectasia (HHT). The authors[1] do not seem to be paying attention to the possible presence of genetic thrombophilic risk in HHT patients in relation to pharmacological treatment. Recently, we published[2] a case of HHT and genetic thrombophilia with pharmacological complications attributed to the coexistence of both genetic conditions.

In the review paper, the authors[1] also highlight the risks of life-threatening maternal complications in pregnant HHT women. It is well known that up to 65% of vascular gestational abnormalities can be accounted for by genetic thrombophilias.[3] Therefore, it is possible that women with HHT may have recurrent pregnancy loss or other pregnancy complications because of to thrombophilic gene mutations. In the presence of thrombophilic risk, therapy with acetylsalicylic acid and low molecular heparin is recommended, but this may increase the risk of haemorrhages in the presence of HHT. To our knowledge, there are no data on the incidence of pregnancy complications, such as fetal loss or venous thrombosis, in HHT patients. As reported by Undas *et al.*,[4] in the absence of life-threatening haemorrhages and detectable vascular malformations, oral anticoagulation could be considered with strictly haematological and clinical follow-up. An associated thrombotic tendency may confer a survival advantage for HHT patients by decreasing the severity of their bleeding problems.[5]

We suggest that for the clinical management of these patients, genetic tests and counselling for inherited thrombophilia may be useful to prevent vascular and pregnancy complications and that more appropriate pharmacological treatment in consideration of the possible presence of both genetic conditions is used.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Reply to Bianca *et al*

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We thank Bianca *et al*[1] for their interesting comments and hereditary haemorrhagic telangiectasia (HHT) case reports. Within our structured 2009 *EJHG* review,[2] we did not have space to discuss in detail all of the implications of the cited studies, including, of relevance here, our large thrombosis[3] and pregnancy[4] HHT data series (*EJHG* references 9 and 48).

Concern regarding thrombophilic risk in HHT patients in relation to pharmacological treatment was one of the main conclusions of our cited (*EJHG* reference 9) series of 309 HHT-affected individuals.[3]