

## Editorial Article

# Novel Agents for the Treatment of Hereditary Hemorrhagic Telangiectasia: Are They Effective Enough?

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## Editorial

Hereditary hemorrhagic telangiectasia (HHT) is a relatively rare (1/5000) autosomal dominant disorder characterised with arteriovenous malformations located in mucosal areas, gastrointestinal tract, pulmonary, hepatic and cerebral circulations. Several mutations (endoglin, activin A receptor type II-like 1, and less frequently *SMAD4* gene) are determined, however the main cause of HHT remains unclear [1, 2]. Current guidelines recommend to take measures for the prevention of bleeding, avoidance of antiplatelet or anticoagulant agents (if possible), electrical or chemical coagulation techniques via endoscopic procedures, and treatment of iron-deficiency anemia [2].

Circulating vascular endothelial growth factor (VEGF) levels are elevated in HHT. Recently bevacizumab, a VEGF inhibitor, was administered parenterally to patients with HHT in order to investigate whether it has systemic anti-angiogenic effects in HHT. The bevacizumab dose administered was the same as its usual dose recommended for metastatic colorectal cancer patients (5 mg/kg, every 2 weeks, for 6 cycles). Among the evaluable subjects (n= 5), all patients had a decrease in transfusion requirements, and one of them gained transfusion independency. Improvement in hemoglobin levels were detected 2 months following bevacizumab administration. Some patients (n= 2) needed additional infusions of bevacizumab, but no serious (grade III or IV) side effects were reported. Bevacizumab was found to be more effective in patients suffering from epistaxis [3]. To avoid its systemic side-effects bevacizumab was also administered locally. In ELLIPSE phase-1 study which was performed on 40 HHT patients, nasal bevacizumab was well tolerated but showed no efficacy at the doses of 12.5, 25, 50, 75, and 100 mg/mL, respectively [4]. Subsequently, in a placebo-controlled and double-blind study with 15 HHT patients, a single intranasal submucosal bevacizumab injection (10 mL, 100 mg) reduced epistaxis severity and visual analog scores (27% vs 3%) non-significantly [5].

Beyond its immunomodulatory effects, thalidomide has anti-angiogenic potency, and also suppresses tumor necrosis factor alpha [1]. The efficacy of thalidomide in preventing gastrointestinal hemorrhages from angiodysplasias was proven in 2011. This prospective study included 2 arms, 100 mg/day thalidomide versus 400 mg/day iron (controls) were administered for 4 months. As expected, the subjects in thalidomide arm had significantly higher response rate which was described as a decrease by  $\geq 50\%$  in bleeding episodes.

Thalidomide treatment was associated with a reduction in VEGF levels without any serious adverse events [6]. These promising results led clinicians to administer thalidomide for patients with HHT. Although no randomised clinical trial is reported, some small case series have emerged its clinical efficacy in HHT patients presenting with epistaxis at a dose of 50-250 mg/day (most commonly 100-200 mg/day). These patients have also showed less transfusion requirements and have described improvements in quality of life scores [7]. Special attention needs be paid while prescribing thalidomide. Teratogenicity, sedation, peripheral sensorial neuropathy, hematologic cytopenias, and venous thrombosis are the potential adverse effects of thalidomide. 100 mg/day thalidomide should be used to avoid from neuropathy instead of 300 mg/day. Interestingly, thromboembolic events were not reported in previous studies including patients with HHT [1].

Lenalidomide, a novel immunomodulatory drug which has less side effects than thalidomide, was successfully used in a 69-year-old woman with chronic gastrointestinal bleeding due to HHT. Initially she was under thalidomide therapy (50-100 mg/day), but the drug was stopped because of thalidomide-induced grade-3 peripheral neuropathy. She has become free of gastrointestinal hemorrhage and drug side effects, with higher hemoglobin values (10.9 vs. 13.2 g/dL) and reduced iron and blood transfusion requirements after a 13-months period of lenalidomide treatment [8]. Both thalidomide and lenalidomide carry anti-angiogenic properties in a dose-dependent manner [9]. Additionally, the inhibitory potency of lenalidomide on growth factor-induced Akt phosphorylation and anti-migratory effects on endothelial cells were clearly shown in a rat mesenteric window assay by Dredge and colleagues [10]. Lenalidomide can suppress bone marrow activity, and therefore individual dosing should be monitored according to regular blood counts. However, high treatment costs, lack of indication in patients with HHT regarding health insurance, and most importantly limited evidence-based data about the efficacy of lenalidomide in HHT should be kept in mind.

In conclusion, novel agents such as bevacizumab or IMiDs should be used cautiously because of their potential side effects. Bevacizumab and thalidomide seems to be effective in HHT patients presenting with epistaxis. However, IMiDs could be preferred in gastrointestinal hemorrhages in HHT. These new treatment options will also provide improvements in quality of life in HHT. Although serious side effects are not reported in the recommended doses of these agents, there is

insufficient evidence to recommend them as first line therapy. Further randomised and well-designed studies are needed to better identify the optimal treatment modality for the prevention and treatment of bleeding episodes in HHT.

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