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Bevacizumab: Finding Its Niche in the Treatment of Heart Failure Secondary to Liver Vascular Malformations in Hereditary Hemorrhagic Telangiectasia

Dupuis-Girod S, *Ginon I*, *Saurin JC*, *Marion D*, *Guillot E*, *Decullier E*, et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. JAMA 2012;307:948-955. (Reprinted with permission.)

Abstract

Context: The only treatment available to restore normal cardiac output in patients with hereditary hemorrhagic telangiectasia (HHT) and cardiac failure is liver transplant. Anti-vascular endothelial growth factor treatments such as bevacizumab may be an effective treatment. Objectives: To test the efficacy of bevacizumab in reducing high cardiac output in severe hepatic forms of HHT and to assess improvement in epistaxis duration and quality of life. Design, Setting, and Patients: Single-center, phase 2 trial with national recruitment from the French HHT Network. Patients were 18 to 70 years old and had confirmed HHT, severe liver involvement, and a high cardiac index related to HHT. Intervention: Bevacizumab, 5 mg per kg, every 14 days for a total of 6 injections. The total duration of the treatment was 2.5 months; patients were followed up for 6 months after the beginning of the treatment. Main Outcome Measure: Decrease in cardiac output at 3 months after the first injection, evaluated by echocardiography. Results: A total of 25 patients were included between March 2009 and November 2010. Of the 24 patients who had echocardiograms available for reread, there was a response in 20 of 24 patients with normalization of cardiac index (complete response [CR]) in 3 of 24, partial response (PR) in 17 of 24, and no response in 4 cases. Median cardiac index at beginning of the treatment was 5.05 L/min/m2 (range, 4.1-6.2) and significantly decreased at 3 months after the beginning of the treatment with a median cardiac index of 4.2 L/min/m2 (range, 2.9-5.2; *P* = .001). Median cardiac index at 6 months was significantly lower than before treatment (4.1 L/min/m2; range, 3.0-5.1). Among 23 patients with available data at 6 months, we observed CR in 5 cases, PR in 15 cases, and no response in 3 cases. Mean duration of epistaxis, which was 221 minutes per month (range, 0-947) at inclusion, had significantly decreased at 3 months (134 minutes; range, 0-656) and 6 months (43 minutes; range, 0-310) (*P* = .008). Quality of life had significantly improved. The most severe adverse events were 2 cases of grade 3 systemic hypertension, which were successfully treated. *Conclusion:* In this preliminary study of patients with HHT associated with severe hepatic vascular malformations and high cardiac output, administration of bevacizumab was associated with a decrease in cardiac output and reduced duration and number of episodes of epistaxis.

Comment

Dupuis-Girod et al.[1] in France recently reported the results of a phase 2 preliminary study demonstrating the efficacy of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor in patients with hereditary hemorrhagic telangiectasia (HHT) and liver vascular malformations (LVMs) leading to symptomatic heart failure.

HHT is a hereditary illness characterized by arteriovenous malformations (AVMs) in many organs. Small LVMs are present in upwards of 70% of patients with HHT, but are usually asymptomatic and detected only on imaging studies.[2] However, LVMs large enough to cause symptoms can occur in ~8% of HHT patients.[3,4] The most common clinical presentation is heart failure resulting from significant hepatic artery to hepatic vein shunting, which leads to excessively high cardiac output (Fig. 1).[4,5] Symptomatic heart failure occurs most commonly in women in their 6th and 7th decades.[4,5]

This high output type of heart failure often manifests as exertional fatigue and dyspnea, and can be diagnosed in the presence of a characteristic triad of a wide arterial pulse pressure, systolic murmur, and liver bruit.[4] The left ventricular systolic function is almost always preserved, due to the low systemic vascular resistance, but symptomatic patients often have left atrial enlargement and pulmonary hypertension develops when the pulmonary vasculature is no longer able to maximally dilate and accommodate the high pulmonary blood flow (Fig. 1). High output failure is often exacerbated by anemia, which is common in patients with HHT due to epistaxis and gastrointestinal bleeding from mucosal AVMs. Symptoms often respond to medical therapy with treatment of anemia, diuretics, and correction of atrial fibrillation.[6,7] The latter often precipitates or exacerbates symptoms due to the loss of atrial contraction and the sole reliance on passive ventricular filling (Fig. 1). In patients who do not respond to medical therapy, embolization or surgical ligation of the hepatic artery has been attempted. While these approaches decrease hepatic blood flow and ameliorate heart failure, the response is often transient and, more important, can be associated with biliary and/or hepatic necrosis, leading to death or the need for urgent liver transplant.[8-10]

Liver transplantation has been utilized with good success for patients with HHT and symptomatic heart failure, particularly in Europe.[9-11] However, the lack of donor organ availability, normal liver synthetic function leading to a low model for endstage liver disease (MELD) score and operative risk of this procedure all limit the wide application of transplant, particularly in older patients and those who do not have a living related donor. Thus, additional approaches to treat LVMs would be highly desirable.

Initial case reports suggested the possibility that bevacizumab, an antiangiogenic drug, might lead to

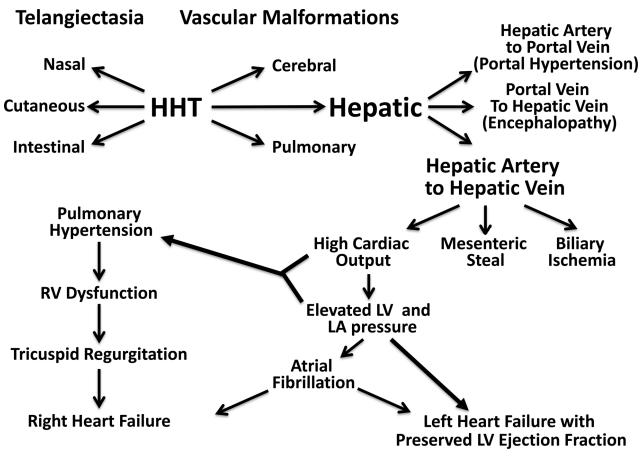

Fig. 1. Major clinical manifestations in HHT syndrome. Sites of telangiectasia and larger vascular malformations are shown. Liver malformations occur most commonly in patients with mutations in the ACVRL1 gene, which encodes the activin receptor-like kinase 1, or ALK1, which is a type I cell-surface receptor in the TGF beta signaling pathway. Large complex hepatic artery to hepatic vein malformations are the most common, although they sometimes can be associated with other intrahepatic malformations, as shown. Hepatic artery to venous malformations lead to high flow "shunts" in the liver that can double or triple resting cardiac output. The cardiac flow eventually leads to elevated pressure in the left ventricle and left atrium, although the low systemic vascular resistance helps to prevent contractile dysfunction and left ventricular ejection fraction is preserved. In contrast, pulmonary arterial pressure becomes elevated, particularly when left atrial pressure rises and the ability of the pulmonary vasculature to dilate is diminished. The combination of high cardiac flow and pulmonary hypertension leads to RV dysfunction, tricuspid regurgitation, and right heart failure. Elevated left atrial pressure leads to the development of atrial fibrillation, which can worsen cardiac hemodynamics with the loss of atrial contraction, promote thrombus formation, and increase the risk of stroke.

regression of LVMs and improve symptoms in HHT patients with high output heart failure.[12,13] However, the French study is groundbreaking in that it is the first to apply this strategy to a cohort of patients under carefully monitored conditions. The study was a nonrandomized trial aimed at investigating the safety and feasibility of bevacizumab treatment in patients with HHT, LVMs, and symptomatic heart failure. The investigators administered bevacizumab every 2 weeks at a dose of 5 mg/kg intravenously for a total of six doses and then assessed echocardiographic estimated cardiac output and pulmonary artery systolic pressure, as well as patients' reported dyspnea, epistaxis, and quality of life measures at 3 and 6 months after the initiation of treatment.

Impressively, 20 of 24 patients had improvement in their cardiac index, which was the primary efficacy outcome. Of these responders, three had normalization of their cardiac index after 3 months of therapy. In addition, there appeared to be improvement in pulmonary hypertension as well as epistaxis and quality of life. As such, the results offer the first glimmer of hope for a novel strategy to reverse the effects of liver AVMs in these patients.

There are several issues that need to be considered to place the findings in an appropriate context. First, the mean cardiac output decreased by only 17%, a modest improvement. Second, the baseline cardiac output was only moderately elevated at 5.1 L/min/m^2 (normal is $<$3.5 L/min/m^2). Third, cardiac output was assessed only by echocardiography. Although echocardiographic readings were carefully performed by a blinded expert reader, cardiac output by this technique is calculated by the product of the left ventricular outflow track diameter, mean left ventricular outflow track flow velocity, and the heart rate. Precise estimates of the outflow track velocity and diameter can be challenging. Even though at least five blood flow velocities and three outflow track diameters were analyzed, the interobserver and intraobserver reproducibility of these measurements was not addressed nor were day-to-day variations. A placebo treatment group would have been valuable to determine the consistency of cardiac output measurements over time, as well as to exclude a placebo effect. There is also a possibility that improvement in cardiac output could have been in part the result of a decrease in anxiety and the level of adrenergic stress over the course of the study.

The investigators recognized the importance of ensuring the safety of their subjects and they employed a two-stage design, analyzing the results on their first seven patients to assure efficacy and safety, before going on to recruit an additional 18 patients. Cancer patients treated with bevacizumab have an increased risk of hemorrhage, thrombotic events, gastrointestinal perforation, and reversible posterior leukoencephalopathy. Side effects are always a concern with new cancer therapies and there were potential issues with the use of bevacizumab in HHT patients. Bevacizumab treatment could be problematic in HHT patients due to their susceptibility to epistaxis and gastrointestinal (GI) bleeding, or potential venous thrombosis and stroke related to paradoxical embolization through pulmonary AVMs. The investigators took measures to avoid risk of hemorrhage by excluding patients with cerebral AVMs or thrombocytopenia and those on anticoagulant therapy. Importantly, they also excluded patients with atrial fibrillation which, as mentioned previously, is a common precipitant of heart failure in these patients.

Fortunately, no serious events were observed during the short-term treatment period. There was one case of grade 3 hypertension ($>$180/110 mmHg), which is

a known complication of antiangiogenic therapy and occurs in up to 16% of cancer patients. This patient was successfully treated with a calcium channel blocker. There were also 89 adverse events, judged as possibly or certainly related to bevacizumab, which included headache in 52 patients, nausea and vomiting in 12 patients, and asthenia, abdominal pain, muscular pain, diarrhea, and rash in a small number of others. Again, a placebo-treated control arm would have been very helpful to clarify the causality of these adverse events.

Advanced therapies should be used in patients who are very symptomatic, do not respond to medical therapy, and/or have a poor short-term prognosis. In the French study, two-thirds of the patients had only mild symptoms based on their New York Heart Association class II dyspnea. The report did not detail the patients' diuretic therapy or renal function, leaving uncertainty as to whether they had been maximally treated with conservative therapy. Although the median hemoglobin at study entry was 120 g/L, the range was wide and one patient had a baseline hemoglobin of 51 g/L. It would appear that a subgroup of patients had significant baseline anemia that might have contributed to their symptoms and might have improved with specific therapies (e.g., blood transfusions, iron infusions, or nasal surgery).

Highly symptomatic patients with HHT are very difficult to treat and an innovative successful strategy would be quite important. As mentioned previously, this particular cohort was somewhat healthier than patients referred to some HHT centers with heart failure from LVMs.[4] They had a median age of 59 years (maximum 68 years) and most lacked echocardiographic evidence of severe pulmonary hypertension (estimated RV systolic pressure median 33 mmHg, maximum 79 mmHg). Also, the study excluded patients with atrial fibrillation, which generally represents an advanced manifestation of the high output heart failure syndrome. Whether bevacizumab would be effective in more advanced patients remains to be investigated.

In moderately symptomatic patients who fail intensive medical therapy, liver transplantation remains the only established approach to prevent progressive heart failure. Bevacizumab might be considered as a bridge to transplantation, except that it inhibits wound healing and the general recommendations are that treatment be discontinued for at least 1 month prior to surgery. This consideration would preclude cadaveric liver transplant, although elective transplantation would still be feasible with a living donor.

The effects of bevacizumab on the liver were carefully evaluated in this study with hepatic computed tomography (CT) scans, Doppler ultrasound, and liver function tests (LFTs). A prior case report had suggested that bevacizumab was associated with a dramatic reduction in liver volume,[12] raising hope that antiangiogenic therapy would lead to substantial remodeling of the liver AVMs. However, the French study did not show any changes in liver volume, hepatic artery diameter, or peak hepatic arterial flow velocity. There was significant prolongation of the transit time between the hepatic artery and the hepatic veins, perhaps demonstrating some effect on vascular remodeling. LFTs in this cohort at baseline showed only expected minor abnormalities, mostly in the alkaline phosphatase. There was no improvement in LFTs and there was some concern that five patients demonstrated an increase in aminotransferase levels to 1.5 times their initial values.

Thus, the French study is a pioneering contribution, supporting the concept that antiangiogenic therapy might be a novel strategy to treat patients with LVMs and symptomatic heart failure. Since many patients respond to standard therapy for heart failure, bevacizumab should ideally be investigated in those who do not respond to more conservative therapy. Additionally, because it was a short-term and nonrandomized trial, more prolonged bevacizumab treatment will need to prove effective and safe in patients with HHT. Whether bevacizumab might be efficacious in relieving other symptoms related to hepatic vascular malformations, such as portal hypertension, biliary ischemia, or hepatic encephalopathy, is a separate issue that also needs to be explored. The results of this study will likely generate enthusiasm to treat selected patients with off-label bevacizumab. However, recognizing the limitations of this study, caution is appropriate. Individual physicians and patients may decide to use bevacizumab on a compassionate basis, which might be appropriate in highly symptomatic and refractory patients who are not candidates for liver transplantation. In other patients, conservative therapies should be the mainstay of therapy until randomized placebo-controlled trials further test this innovative strategy.

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