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REVIEW

Hepatic manifestations of hereditary haemorrhagic telangiectasia

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Abstract

Hereditary haemorrhagic telangiectasia is a genetic condition of abnormal blood vessel formation resulting from an imbalance of pro- and anti-angiogenic products of the transforming growth factor β/bone morphogenetic protein signalling pathway which contributes to vascular remodelling and maintenance. Hepatic vascular malformations are common although less frequently symptomatic, but may result in high-output cardiac failure, portal hypertension and biliary ischaemia. Whilst the understanding of the genetic and cell signalling pathways that are the hallmark of hereditary haemorrhagic telangiectasia have been clarified, there remain challenges in therapy for these patients. Only patients with symptomatic hepatic vascular malformations require treatment, with most (63%) responding to first-line medical therapy. For non-responders, bevacizumab is effective in reducing cardiac output in those with heart failure secondary to hepatic vascular malformations as well as other manifestations of the disease. Although liver transplantation is the only curative option, optimal timing is critical. Novel anti-angiogenetic drugs and those that target aberrant cell signalling pathway are being explored.

KEYWORDS
angiogenesis, hereditary haemorrhagic telangiectasia, liver transplantation, vascular malformation, VEGF

1 | INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT), also known as Rendu Osler Weber syndrome, is an autosomal dominant condition that results in abnormal blood vessel formation.[1] HHT can be classified by type based on the genetic mutation and clinical features, with type 1 (HHT1) and 2 (HHT2) encompassing most cases. It affects approximately 1 in 5000–8000 individuals worldwide, with regional variations including in the clinical manifestations most commonly seen. HHT1 is seen more in North America and Europe, and HHT2 is more likely in Mediterranean areas and South America.[2]

The hallmarks of HHT are telangiectasia, vascular malformations (VMs) and bleeding. Telangiectasia occur on mucocutaneous surfaces such as skin, the gastrointestinal tract and buccal mucosa. VMs occur in internal organs such as the liver, lung and brain. The severity, age of onset and locations of the vascular lesions are variable. The most common clinical manifestation is spontaneous and recurrent epistaxis beginning at 12 years of age.[3] Approximately 25% of HHT patients will have gastrointestinal bleeding which most commonly begins after 50 years of age.[3] Diagnosis is based on consensus clinical diagnostic criteria, the Curaçao criteria, from the Scientific Advisory Board of the HHT Foundation International Inc.[4] A definite diagnosis

of HHT can be made on the basis of at least three of the four criteria listed in Table 1.

2 | GENETIC MUTATIONS AND GENOTYPE PHENOTYPE CORRELATION

HHT is an autosomal dominant disease from mutations mainly in endoglin, *ENG*, (HHT1) or activin A receptor like 1, *ACVL1*, (HHT2) genes which account for the vast majority of cases.[5,6] These *ACVRL1* and *ENG* genes encode a bone morphogenetic protein (BMP) receptor activin receptor like kinase 1 (ALK1) and a co-receptor for the transforming growth factor (TGF) beta family called endoglin, respectively.[5,6] Mutations in the mother against decapentaplegic homologue 4, *SMAD4*, gene (that encodes components of the BMP9/ALK1 signalling pathway) have been described in a subset of HHT patients with a juvenile polyposis/HHT overlap syndrome (JP-HHT), but the frequency of these mutations in the HHT population is small (up to 2%).[7–9] More recently, there has been identification of variants in the growth differentiation factor 2 (*GDF2*) gene which encodes BMP9 that is associated with lower plasma BMP9 levels and pulmonary AVMs.[10] There remains a minority of patients who meet clinical criteria for HHT diagnosis but who do not have one of the recognised mutations. Furthermore, the 100 000 Genome project designed to identify genetic variants that cause rare, inherited diseases has seen recent reports identifying low-grade mosaicism through bidirectional whole genome sequencing in HHT patients.[11] These patients had an established HHT diagnosis by Curaçao criteria and were presenting as the index case in their family.[11]

HHT exhibits incomplete penetrance, and clinical manifestations vary between and within families both in onset and severity of disease, even from the same mutation. There is a degree of genotype–phenotype correlation in HHT1 and HHT2 patients, but there remains variability.[12]

Molecular genetic testing can be offered to at risk family members if the particular mutation is known. Molecular genetic testing approaches can include serial single gene testing, use of a multi-gene panel and a more comprehensive genomic testing.

The role of genetic testing is gaining prominence in the diagnosis of HHT, particularly as the genetic diagnostic rate has been shown to be similar in those with 3 or 1–2 Curaçao criteria in a cohort of pulmonary AVM patients.[13] It should be remembered that while negative gene testing for HHT does not exclude the diagnosis, positive genetic testing is confirmatory, regardless of symptoms. Genetic testing should be offered as part of the work up for patients with suspected HHT who do not otherwise meet diagnostic criteria.

This reinforces the increasing importance of identifying mutations and offering genetic testing in patients to diagnose HHT, particularly where the classical clinical features are subtle.

Key points

1. Hepatic vascular malformations in hereditary haemorrhagic telangiectasia (HHT) are common, but often asymptomatic.
2. Doppler ultrasound allows characterisation and staging of hepatic vascular malformations.
3. Echocardiography should be performed in those with hepatic manifestations of HHT.
4. Symptomatic hepatic manifestations can be treated with medical therapy, with Bevacizumab second line. Novel therapeutic agents are being developed.
5. Liver transplantation is the only curative option for those who do not respond to medical therapy.

3 | PATHOPHYSIOLOGY

Vascular endothelial cells are regulated by pro- and anti-angiogenesis factors with a change in the balance of these factors triggering either active angiogenesis or vascular quiescence (see Figure 1).[14] HHT can be described as an imbalance between antiangiogenic factors (such as BMP9) and proangiogenic factors (such as vascular endothelial growth factor; VEGF).[15] VEGF is a regulator of angiogenesis and is upregulated in a variety of states including malignancy and inflammatory conditions.[16] Vessels formed by VEGF are abnormal, similar to those seen in HHT.[16]

Abnormal plasma concentrations of TGF-β and VEGF occur due to alterations in the cell signalling pathway as a consequence of the

TABLE 1 The Curaçao criteria for HHT diagnosis.[3]

Epistaxis	Spontaneous and recurrent
Family history	A first-degree relative with HHT
Telangiectasia	Multiple telangiectasia at characteristic sites (lips, buccal mucosa, fingers and nose)
Visceral lesions	Including gastrointestinal telangiectasia (± bleeding); pulmonary, hepatic, cerebral or spinal AVMs
	Definite HHT: 3 criteria Suspected HHT: 2 criteria Unlikely HHT: <2 criteria

Abbreviations: AVMs, arteriovenous malformations; HHT, hereditary haemorrhagic telangiectasia.

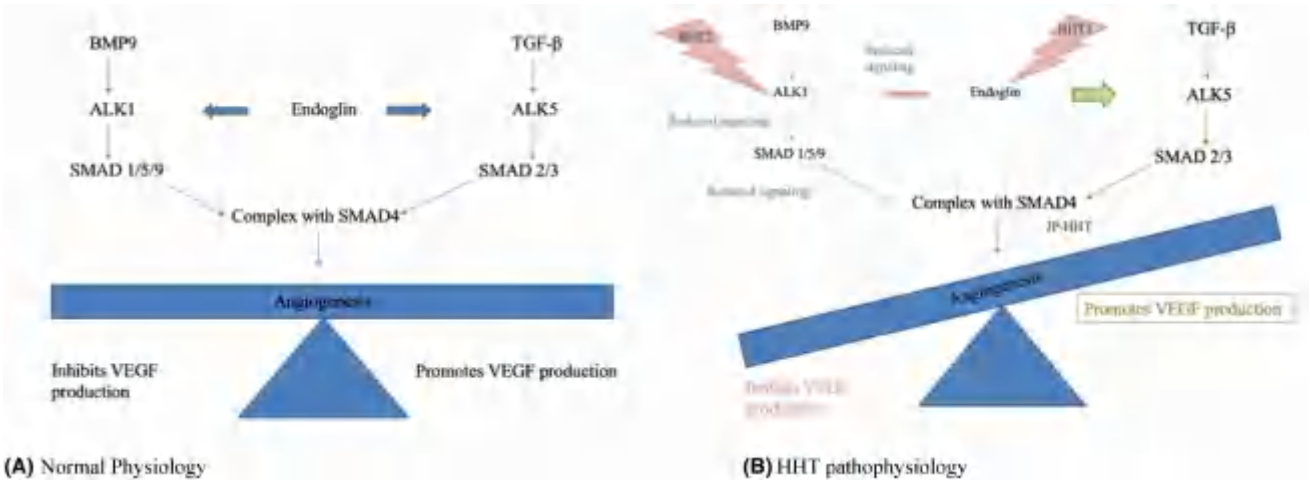

FIGURE 1 Overview of the signalling pathway for VEGF and its effect on angiogenesis (A) shows the normal physiological state with balance between pro- and anti-angiogenic factors. BMP9 activates ALK1 aided by the co-receptor endoglin and TGF-β activates ALK5 with resultant activation of intracellular SMAD pathways regulating VEGF. (B) shows the pathological changes in HHT where mutations affecting BMP9, ALK1 or endoglin cause reduced ALK1 signalling resulting in increased ALK5 signalling and ultimately increased VEGF levels. ALK, activating receptor like kinase; BMP9, bone morphogenetic protein 9; HHT, hereditary haemorrhagic telangiectasia; JP-HHT, juvenile polyposis hereditary haemorrhagic telangiectasia; SMAD, mother against decapentaplegic homologue; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

recognised HHT mutations in *ENG*, *ACVRL1* and *SMAD4* genes. All of these contribute to cell signalling via the TGF-β/BMP signalling pathway which contributes to cell growth and differentiation as well as vascular remodelling and maintenance. It is notable that the products of these mutated genes seen in HHT patients are all loss of function mutations within the same signalling pathway (BMP9/10) with any mutation in this (BMP9, ACVRL1, ENG and SMAD4) resulting in elevation of VEGF through reduced ALK1 pathway signalling (see Figure 2). The main result of BMP9/10 signalling is vascular quiescence.[17,18] Recently, mutations in the growth differentiation factor 2 (*GDF2*) gene (encoding BMP9) have been described in a vascular syndrome with phenotypic features of HHT but the contribution of GDF2 mutations to HHT is estimated to be less than 1%.[19,20]

4 | CLINICAL MANIFESTATIONS

The variability in clinical features of patients with HHT in terms of distribution, severity and complications means that there are likely to be local factors that contribute to any underlying phenotype. These other factors could be the influence of other modifier genes, repeated tissue injury and chronic inflammation.[21,22] An abnormal endothelium may also lead to impaired synthesis of von Willebrand factor and prolonged bleeding.[23]

HHT shows age-related penetrance with increased clinical manifestations developing over time. However, there are common patterns with epistaxis onset often earlier in the disease course and predating telangiectasia and cerebral arteriovenous malformations (AVMs) often congenital.[24–26] A summary of the recommended baseline screening investigations is shown in Table 2.

HHT1 from a mutation in *ENG* is more associated with pulmonary and cerebral AVMs. Epistaxis tends to occur at a younger age, and pulmonary AVMs appear at an earlier age as well as being more frequent.[12] HHT2 resulting from *ACVRL1* mutation is more associated with liver and spinal VMs as well as epistaxis and pulmonary hypertension as summarised in Table 3.[27] Mutations in *SMAD4* result in JP-HTT associated with gastrointestinal polyps, pulmonary hypertension and pulmonary VMs.[26]

At a population level, HHT patients have reduced life expectancy but this is dependent on the extent of the disease, with some patients having a normal life expectancy. A case-controlled study utilising a UK database compared 675 HHT patients with age and gender matched healthy controls found that HHT patients were more likely to have cerebral abscess, migraine, stroke, heart failure, colon cancer and bleeding complications with a hazard ratio for death in HHT patients of 2.03.[28]

Patients with a diagnosis of HHT should be under regular review even where asymptomatic, with a schedule depending on hepatic VMs stage. The review should include clinical evaluation for any symptoms or signs that could relate to HHT. Full blood count will highlight anaemia, echocardiogram will reveal changes of concern in the asymptomatic patients and pulmonary VMs should be screened for at least every 5 years.

5 | HEPATIC INVOLVEMENT IN HHT

Hepatic VMs are seen in up to 74% of HHT patients, whereas only 8% are symptomatic at diagnosis.[29,30] Average mortality and morbidity rates due to liver VMs were 1.1 and 3.6 per 100

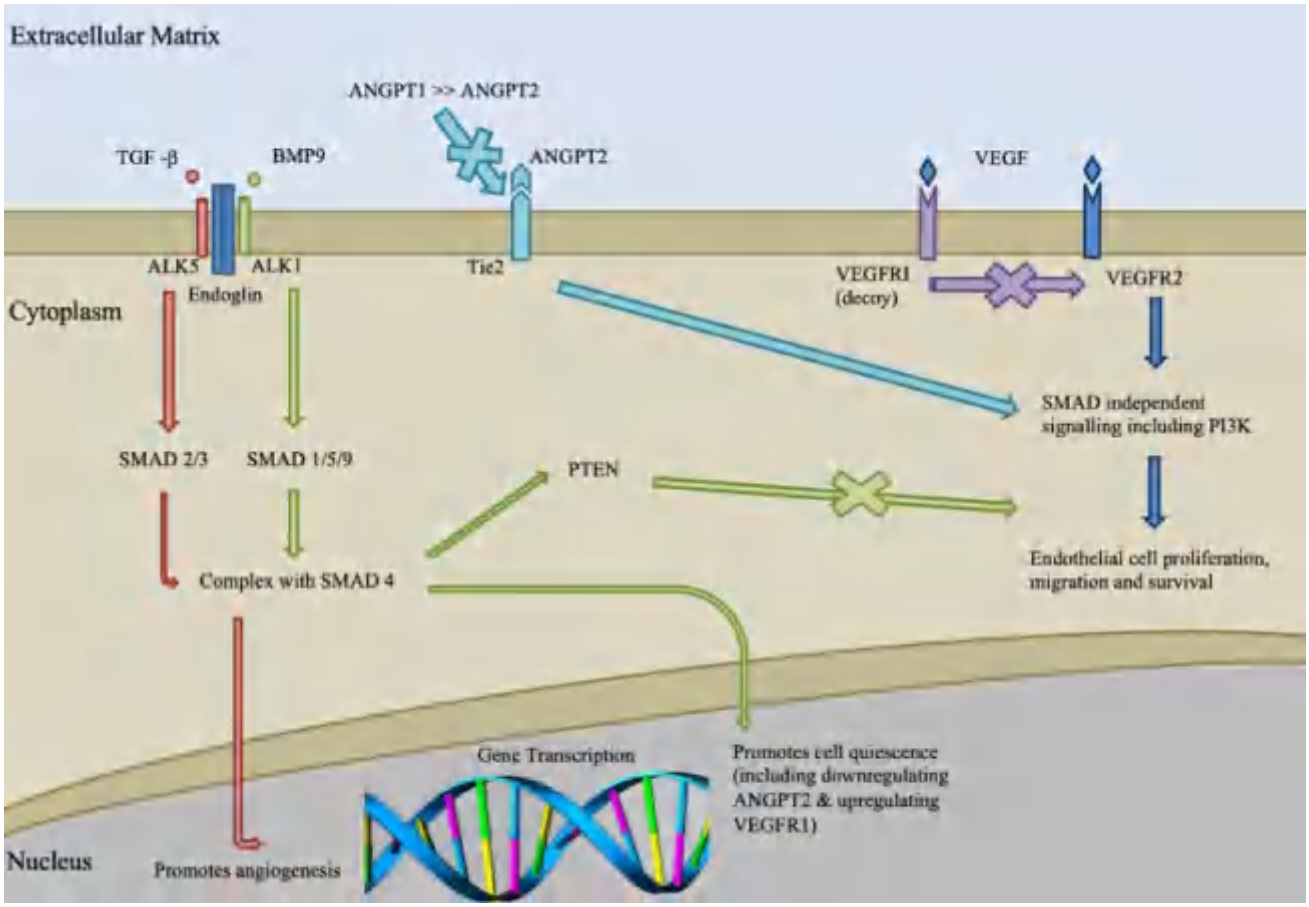

FIGURE 2 Cell signalling pathway outlining the main pathways of both pro- and anti-angiogenic factors that are involved in the pathophysiology of HHT. Vascular quiescence occurs when BMP9 binds to the ALK1 receptor resulting in phosphorylation of SMAD 1/5/9. This in turn combines with SMAD4 ultimately resulting in transcriptional alterations leading to upregulation of VEGF1 which is a decoy that inhibits the pro-angiogenic effects of VEGF2 signalling. Simultaneously, ANGPT2 is downregulated. When ANGPT1 is present in higher levels than ANGPT2, it blocks activation of SMAD independent processes, particularly PI3K, through the Tie2 receptor which is pro-angiogenic. A further effect of the ALK1/BMP9 pathway is maintaining PTEN in its active form which blocks downstream effects of PI3K. ANGPT2, angiopoietin 2; ALK, activating receptor like kinase; BMP9, bone morphogenetic protein 9; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue; SMAD, mother against decapentaplegic homologue; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

TABLE 2 Screening recommendations in newly diagnosed or suspected HHT patients.[22]

Baseline investigations in newly diagnosed or suspected HHT patients:
1. Anaemia and iron deficiency screening at least annually
2. Screening for liver VMs by ultrasound scan if asymptomatic
3. Discuss the pros and cons of brain MRI to search for cerebral VMs
4. Transthoracic contrast echocardiogram± lung CT scan
5. Propose genetic testing

Abbreviations: CT, computed tomography; HHT, hereditary haemorrhagic telangiectasia; MRI, magnetic resonance imaging; VMs, vascular malformations.

TABLE 3 Summary of the genotype–phenotype correlation seen in HHT1 and 2.

	HHT1	HHT2
Epistaxis	+++	+++
GI bleeding	+	++
Liver VMs	+	++
Pulmonary VMs	++	+
Cerebral VMs	++	+
Spinal VMs	–	+

Abbreviations: HHT, hereditary haemorrhagic telangiectasia; VMs, vascular malformations.

person-years, respectively, in a longitudinal cohort.[31] They are more common and tend to be more severe in HHT2.[32] The mean age at diagnosis of liver VMs is 48 years and is more common in females.[31,33] Doppler ultrasound scan of the liver is the first-line imaging technique in patients with HHT due to its safety, tolerability, low costs and accuracy for the detection of liver VMs.[26] This allows characterisation and staging of any liver VMs (see Figure 3; Table 4). Early changes seen with ultrasound scan include dilation

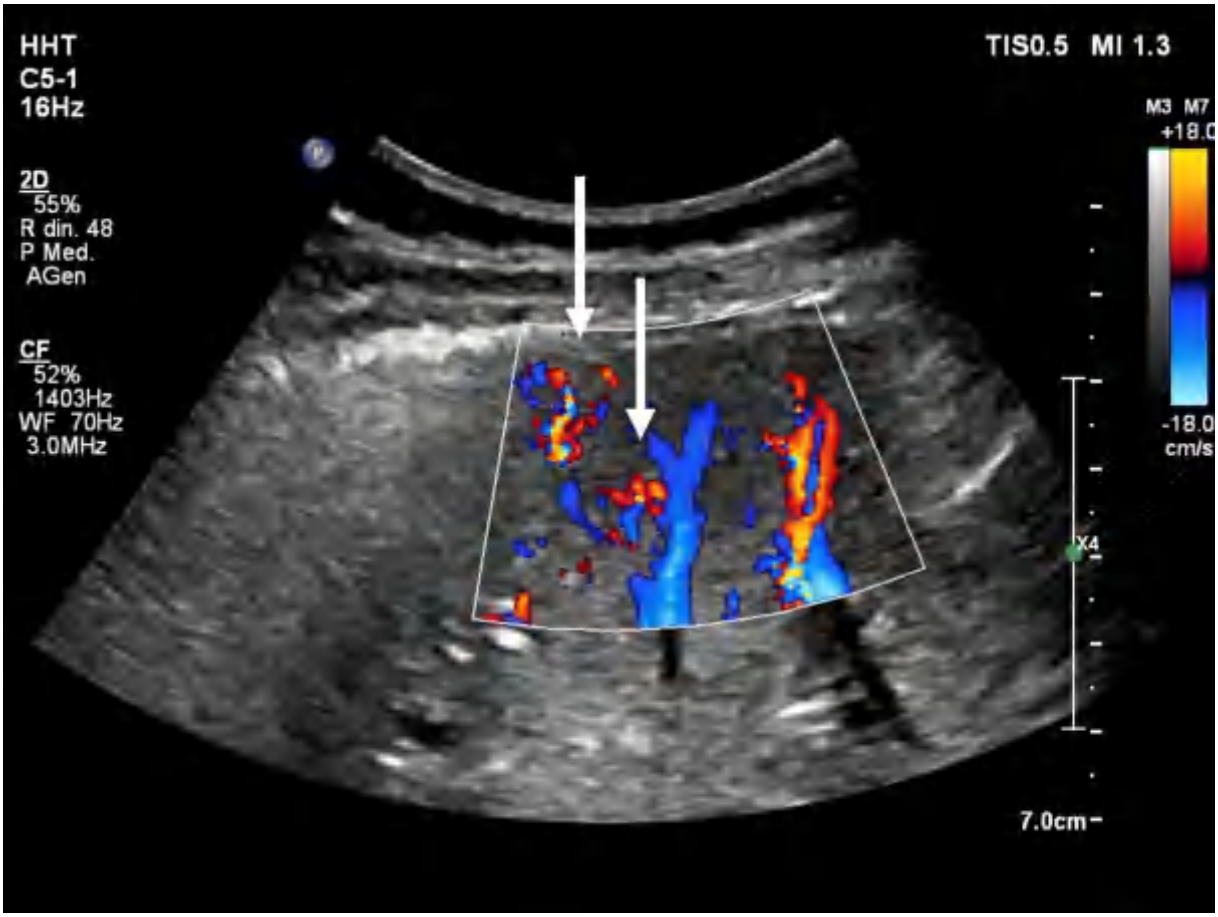

FIGURE 3 High-frequency colour Doppler study of the liver in a HHT patient can show the presence of multiple peripheral VMs (arrows).

of the hepatic artery (see Figure 4) and a low resistivity index (see Figure 5). Ultrasound scan is also effective at characterising later stage VMs (see Figure 6).

Wherever expertise in Doppler US is lacking, multiphase CT can be used, particularly for investigation of symptomatic liver VMs in HHT. CT may also be required, depending on either the presence of focal liver lesions or on the severity of liver VMs and their haemodynamic impact; it is always used in complicated liver VMs considered for LT, particularly the most ominous complication of liver VMs in HHT, that is, necrotising cholangitis with formation of bilomas. MR imaging can also show hepatic VMs. The abnormalities are better depicted on MR angiograms and dynamic MR images, providing a map of anomalous vessels and analysis of filling kinetics; MR has been proven to be as accurate as multirow CT over which it has the advantage of the absence of ionising radiation. Echocardiography should be performed when liver VMs are found to provide information on their haemodynamic consequences.[34] Liver biopsy should be avoided due to the risk of bleeding.

Liver VMs typically present as small diffuse lesions throughout the liver more than discrete large VMs. Three types of intrahepatic shunting can be seen (Table 5); (1) hepatic artery to hepatic veins; (2) hepatic artery to portal veins and (3) portal veins to hepatic veins, leading to different and potentially overlapping clinical features including portal hypertension (PH) with ascites and variceal bleeding; biliary ischaemia with possible subsequent necrosis and high-output cardiac failure (HOCF) (see Figures 7 and 8).[35,36] Perfusional changes within the liver (see Figure 9) may also lead to nodular regenerative hyperplasia and focal nodular hyperplasia.[37] Evaluation of liver lesions can be complex in HHT patients. Firstly, the liver can erroneously appear cirrhotic due to the alterations in hepatic blood flow and resultant diffuse or focal hepatic regenerative activity, so called pseudocirrhosis (see Figures 9 and 10). Secondly, this altered hepatic blood flow may also make interpretation of the vascular characteristics of a liver lesion more difficult to interpret, with examples of liver lesions shown in Figures 11 and 12.[38] Whilst there have been case reports of hepatocellular carcinoma in HHT patients, both in those with and without an additional risk factor, it is rare.[39–41]

Most patients are asymptomatic and do not need treatment for hepatic VMs. The commonest clinical manifestation in those who display symptoms is high-output cardiac failure (HOCF), but complicated PH occurs at a rate comparable to that of HOCF (1.4 and 1.2, per 100 person-years, respectively); HOCF and complicated PH each account for about half of hepatic VM-associated fatalities.[31] HOCF occurs due to intrahepatic shunting, thus the importance of echocardiographic monitoring to assess cardiac output.[42] Anaemia, particularly where difficult to control epistaxis

TABLE 4 Ultrasound grading of hepatic VMs.[33]

VM grading	Ultrasound features
0+	Hepatic artery diameter 5–6 mm and/or Peak flow velocity >80 cm/s and/or Resistivity index <.55 and/or Peripheral hepatic hypervascularisation
1	Hepatic artery dilation, only extrahepatic >6 mm and Peak flow velocity >80 cm/s and/or Resistivity index <.55
2	Hepatic artery dilation extra- and intrahepatic and Peak flow velocity >80 cm/s Possible association with moderate flow abnormality of hepatic artery ± portal veins
3	Complex changes in the hepatic artery and its branches with marked flow abnormalities associated with: -moderate dilatation of hepatic ± portal veins -abnormality of hepatic ± portal vein flow
4	Decompensation of arteriovenous shunt such as: -marked dilation of hepatic ± portal vein -marked flow abnormalities on both arteries and veins

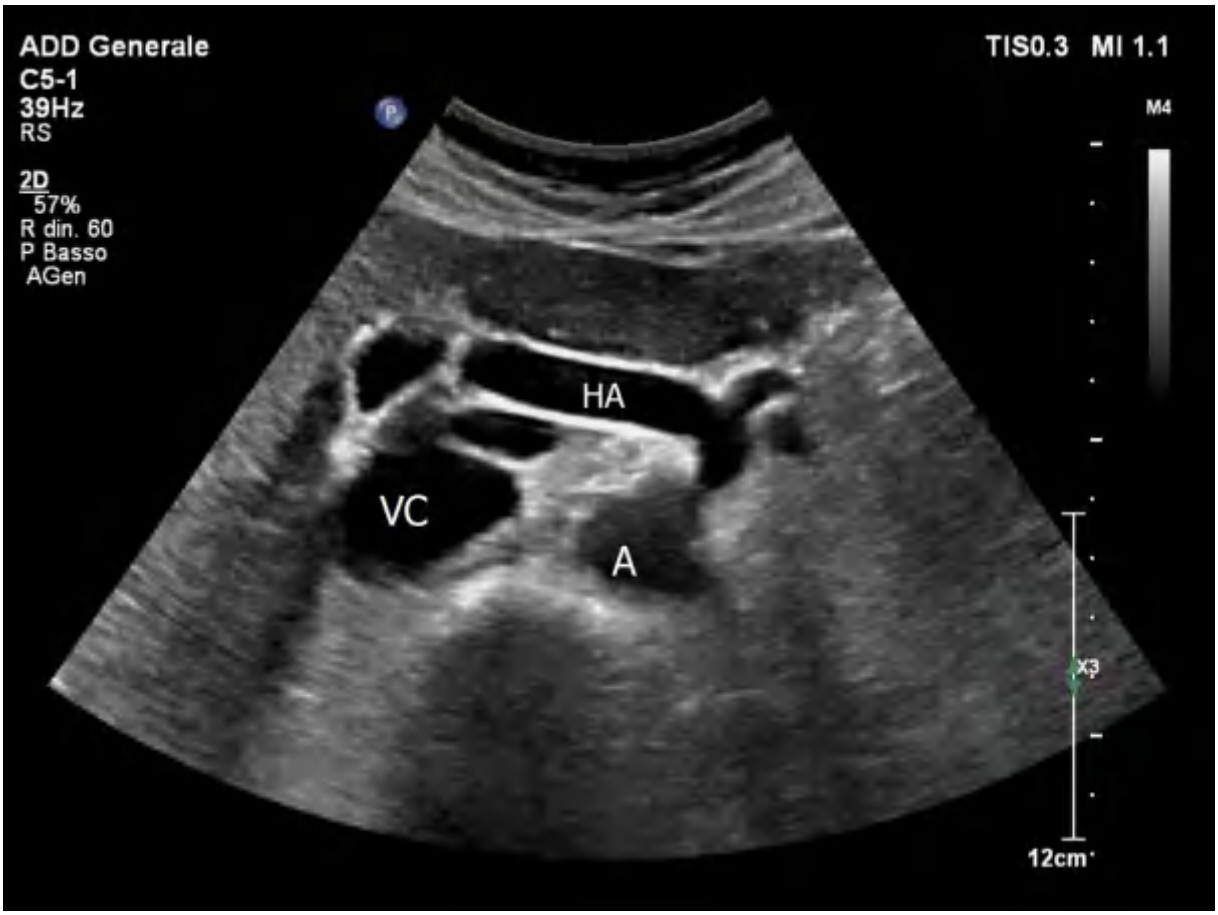

FIGURE 4 Early stages of HAVMs ultrasonography can show dilatation of hepatic artery (HA, in the figure 8 mm). A, aorta, VC, vena cava.

is a feature, can exacerbate this. In liver involvement, HOCF principally occurs from hepatic artery to hepatic vein shunting.[36,43] The VMs have increased blood flow which in turn can cause vascular dilation and also reduced vascular resistance. This leads to attempted cardiac compensation for the resultant fall in blood pressure with an increase in cardiac output and heart rate. Echocardiography should be performed in patients with hepatic VMs to assess their haemodynamic significance, with particular attention paid to cardiac index and pulmonary artery pressures. Where patients describe symptoms of heart failure, or when

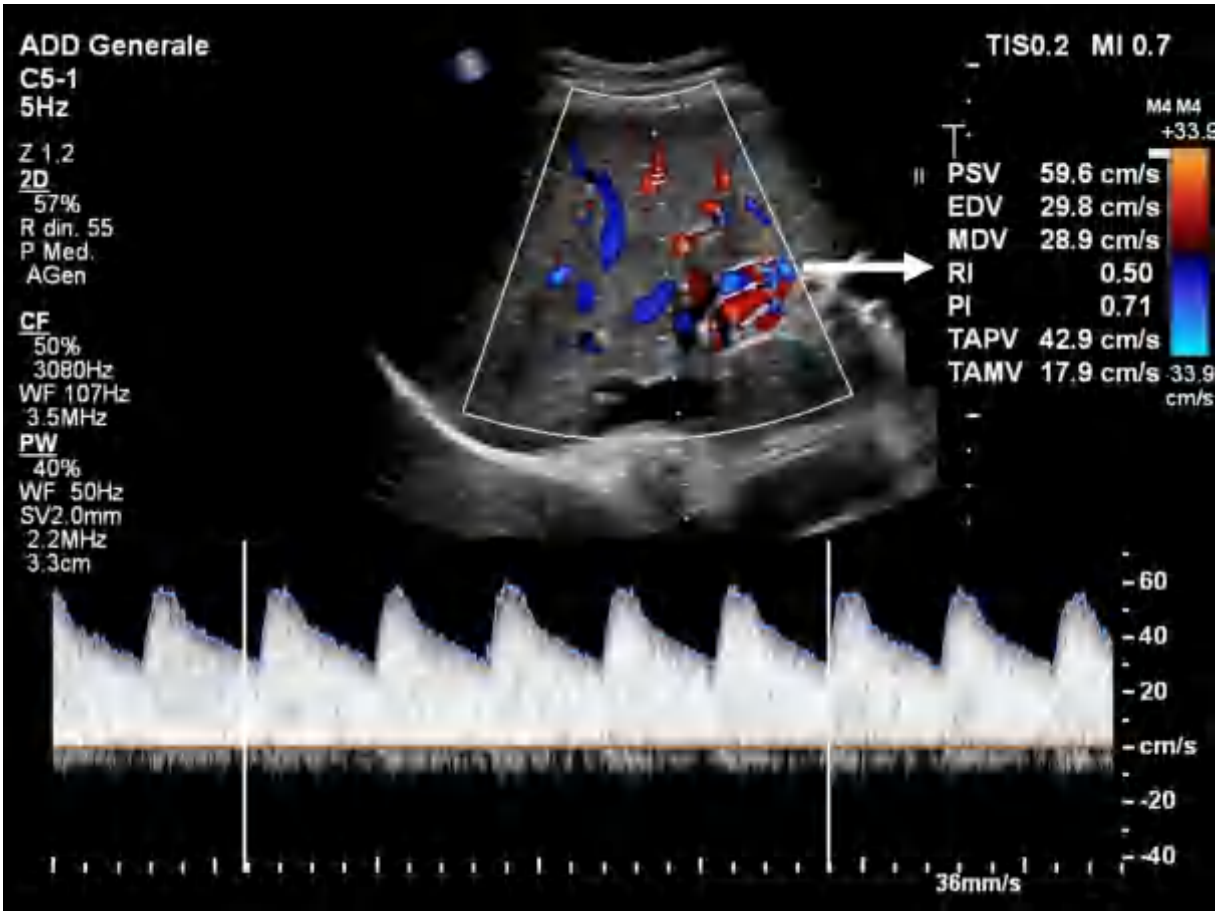

FIGURE 5 Colour Doppler study of intrahepatic arterial flow shows a low resistivity index (RI, arrow) consistent with the presence of intrahepatic AV shunting. Note prominent intrahepatic vessels.

echocardiogram suggests an intermediate or high probability of pulmonary hypertension, right heart catheter studies should be performed. Anicteric cholestasis is observed in one-third of patients with liver VMs and correlates with the severity of VMs and their complications.[31,44,45] Much rarer presentations of liver VMs in HHT are encephalopathy, mesenteric angina and ischemic cholangitis.

Predictors for the development of significant disease from liver VMs include HHT 2 genotype, stage IV liver VMs, (as shown by Doppler ultrasound, Table 4) both of which were prospectively developed.[31] Retrospective analysis has also identified the following factors as predictive of significant disease: age at presentation greater than 47 years; female gender; haemoglobin at presentation and serum alkaline phosphatase more than 300 IU/L.[45] MRI can provide a thorough anatomical assessment of hepatic VMs, however, CT findings do not correlate with liver VM severity or clinical manifestations.[46–48]

In a longitudinal cohort, all eight patients who died had stage 4 liver VMs at baseline, which was a significantly greater mortality rate (p .001) than in patients with other liver VMs stages between .5 and 3. The absolute mortality rates in the symptomatic patients was 15% versus 4% in asymptomatic patients at diagnosis; also, a significantly better outcome was seen in treatments given to the subgroup of patients who were asymptomatic at baseline. Altogether these data confirm that patients with severe hepatic VMs, particularly if symptomatic, have a worst outcome than patients with milder stages of hepatic VMs. HHT patients with hepatic VMs showed also a significantly greater morbidity than controls without hepatic VMs.[31]

6 | TREATMENT OPTIONS

Most individuals with symptomatic hepatic VMs can be managed with medical therapy,[31] whereas asymptomatic cases do not require treatment.

6.1 | First line medical therapy

6.1.1 | HOCF

High-output cardiac failure is managed with diuretics, salt restriction, treatment of anaemia and control of any arrhythmia such as atrial fibrillation including risk assessment for anticoagulation.[36] These patients should be managed by those experienced in HOCF.[26]

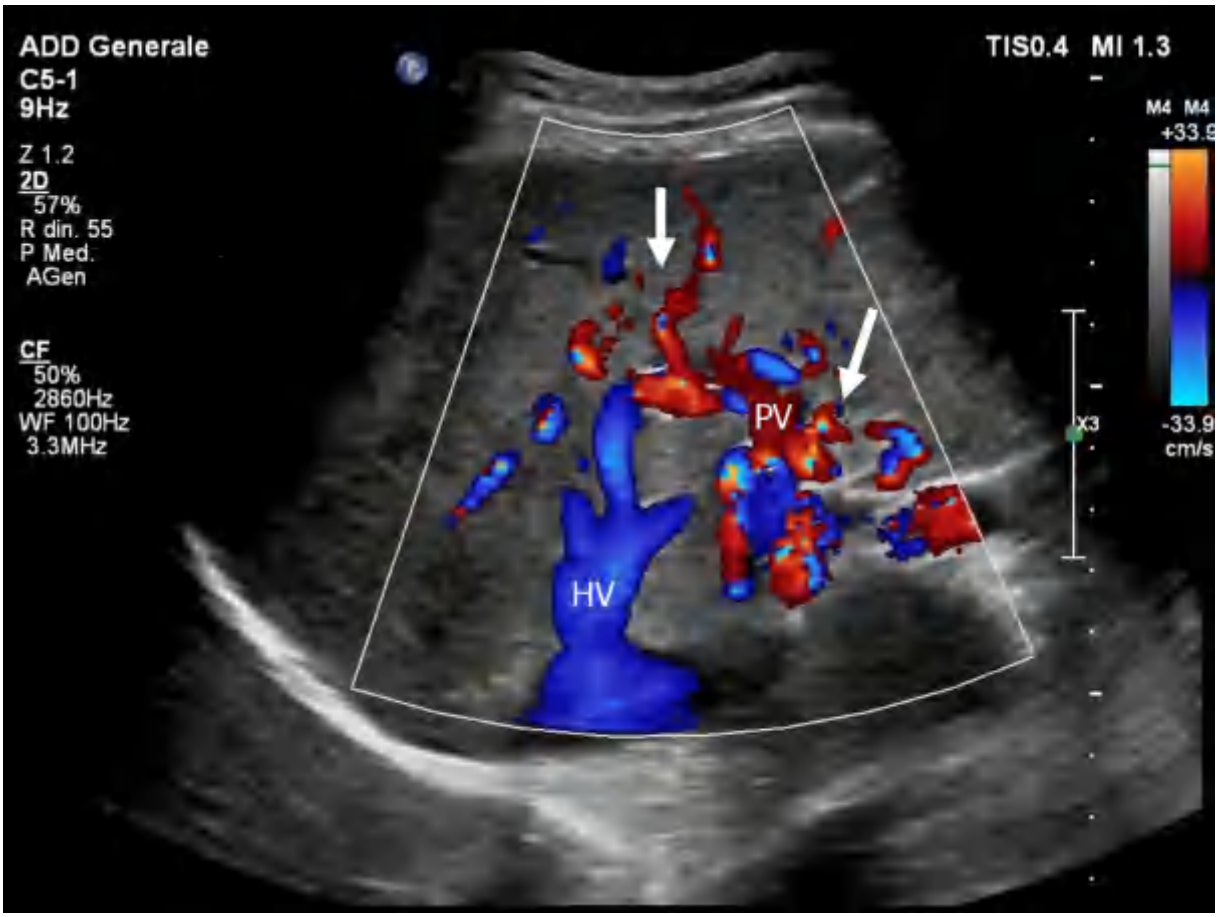

FIGURE 6 In stage 4, HAVMs colour Doppler ultrasonography can show dilation of hepatic veins (HV), prominent and tortuous intrahepatic artery branches (arrows), also surrounding portal vein (PV). Note heterogeneity of hepatic parenchyma.

TABLE 5 Type of hepatic VM and predominant clinical manifestation.

Type of VM	Clinical Manifestation
Arteriovenous	HOCF Biliary ischaemia
Arterioportal	Portal hypertension Biliary ischaemia
Porto venous	HOCF Hepatic encephalopathy

6.1.2 | Portal Hypertension

Portal hypertension and hepatic encephalopathy should be treated in a similar manner to patients with cirrhosis. Ascites is managed with sodium and fluid restriction and the use of diuretics (spironolactone with or without furosemide) and large volume paracentesis in refractory cases.[49] Screening for varices should be performed and if present, managed with beta blockers or endoscopic band ligation if medication is contraindicated or not tolerated.[50] Hepatic encephalopathy management is the same as in patients with cirrhosis and includes treatment with lactulose and rifaximin as well as identifying and treating potential triggers such as electrolyte disturbance, bleeding and infection. Caution may be required with the use of non-selective beta blockers in patients with severe HOCF and they should be used only after consultation with the treating cardiologist. Additionally, transjugular intrahepatic portosystemic shunt insertion for either ascites or bleeding may worsen the hyper dynamic circulation and precipitate cardiac failure and so should be avoided.

6.1.3 | Biliary complications

Antibiotic treatment is used in HHT patients with cholangitis. Endoscopic retrograde cholangiopancreatography (ERCP) and stenting has a limited role as large duct obstruction is not usually present and ERCP has a risk of infection especially in ischaemic ducts. Patients with biliary necrosis have a poor prognosis. Necrotising cholangitis with potential biloma formation and hepatic necrosis is a rare and particularly severe complication of hepatic VMs with high mortality rates which has prompted treatment with urgent liver transplantation.[51]

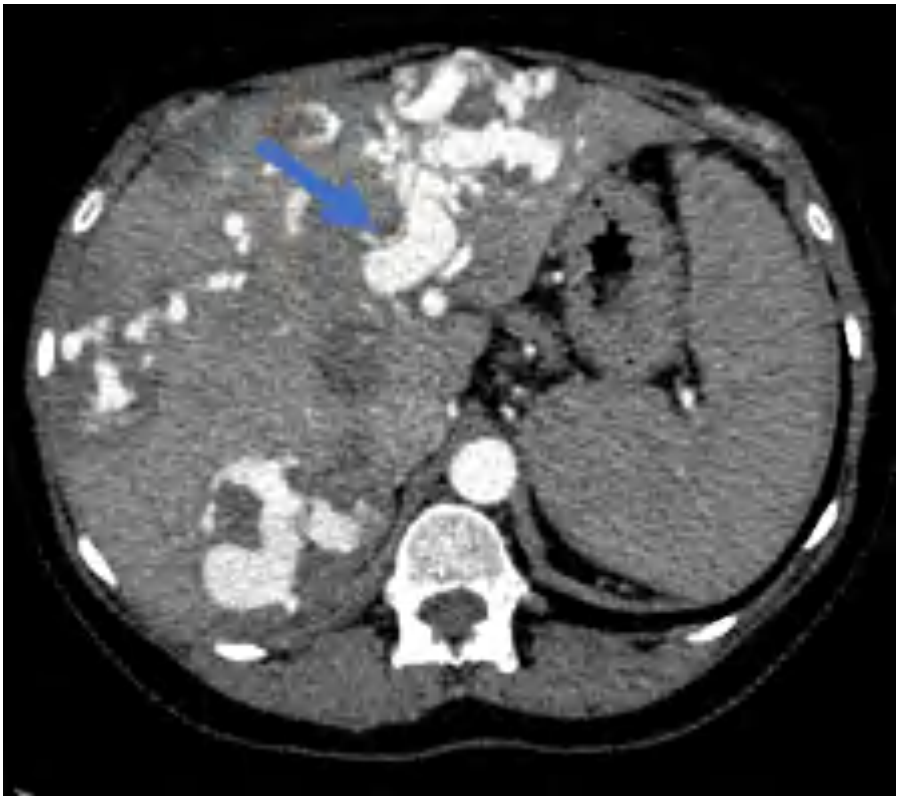

FIGURE 7 Arterio-portal shunting showing opacification of intrahepatic portal vein branches (blue arrow) during the arterial phase of image acquisition.

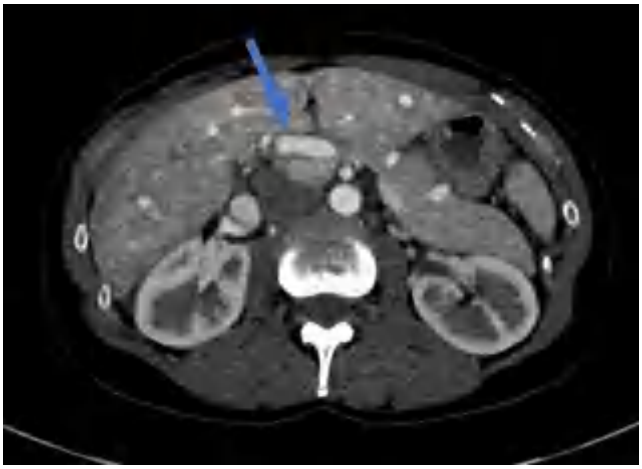

FIGURE 8 Enlarged hepatic artery (blue arrow) from increased blood flow due to the hyperdynamic circulation in a HHT patient.

6.2 | Second line medical therapy

The majority of patients managed in accordance with the first-line medical therapies outlined above show a complete treatment response (63%), with a partial response in a further 21%.[31] Relatively few do not respond to these treatments with death in 14%, all of whom had stage 4 disease at baseline.[31]

For those who fail the above medical therapies, there has been increasing use of Bevacizumab, a recombinant humanised monoclonal antibody designed to inhibit tumour induced neo-angiogenesis through VEGF inhibition.[52] It prevents endothelial proliferation and induces cell death and so both inhibits blood vessel growth and causes regression of existing blood vessels.[53] It is administered intravenously and because HHT is a multivisceral disease, systemic therapy should be beneficial although there have been attempts to use it topically particularly for epistaxis. Adverse effects include hypertension, proteinuria, venous thromboembolic disease, intestinal perforation and poor wound healing.

Although Bevacizumab was initially used as treatment for malignancy, it was noted that in those who also had HHT there was improvement in epistaxis and cardiac failure.[42,54] This led to further study on the efficacy of Bevacizumab in HHT patients with symptomatic liver manifestations associated with high cardiac output and reported results after 6 months follow-up.[43] Patients with cerebral AVMs were excluded.[43] Analysis of 24 patients showed a response in 20 with normalisation of cardiac index in 3 and partial response (any reduction in cardiac output) in 17. There was no response to Bevacizumab in four of the patients.[43] Overall, there was a significant decrease in cardiac output measured by echocardiography from baseline (median 5.05 L/min/m^2) to 3 months (median 4.2 L/min/m^2 $p < .001$) and 6 months (median 4.1 L/min/m^2) at 6 months.[43] Mean duration of epistaxis also improved ($p = .008$) from 221 min per month (range 0–947) initially to 134 min at 3 months (range 0–656) and 43 min at 6 months (range 0–310).[43] Clinical improvements were seen in dyspnoea and normalisation of pulmonary pressure in patients with pulmonary arterial hypertension before treatment were also seen.[43]

Thus, bevacizumab can be considered for patients with symptomatic high-output liver VMs who fail to respond sufficiently to

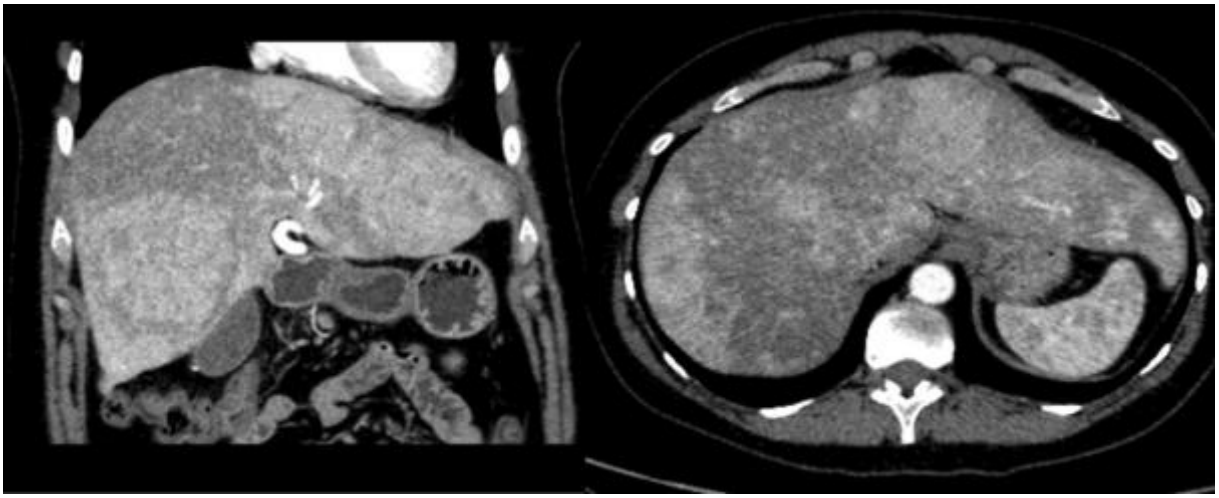

FIGURE 9 Coronal and Axial slices through CT scan imaging of a patient with HHT demonstrating the perfusional changes that can occur.

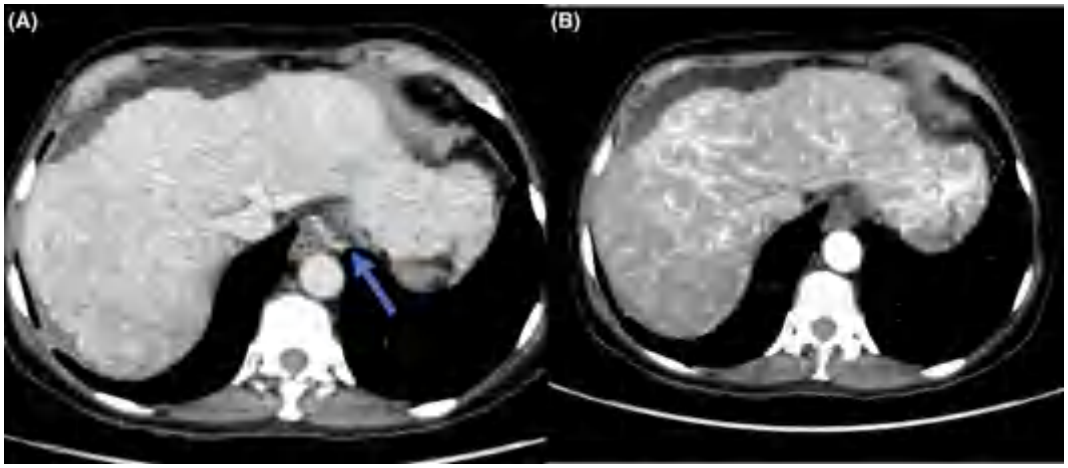

FIGURE 10 Venous (A) and arterial phase (B) images of an HHT patient demonstrating pseudo cirrhosis and varices (blue arrow) with abnormal arterial perfusion respectively.

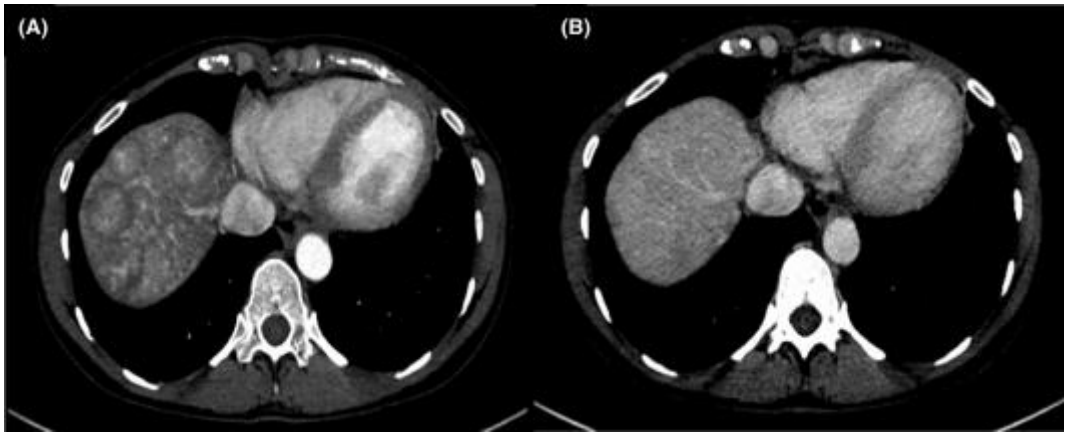

FIGURE 11 Liver lesions showing enhancement in the arterial phase (A) with washout in the porto-venous phase (B).

first-line treatment and are not candidates for liver transplantation.[26] In addition, it has also been shown to be effective in treating bleeding and thus anaemia that occurs in HHT patients.[1,55–60]

A proposed regimen for the use of intravenous bevacizumab is an induction regimen, given at 5 mg/kg at 14–21 day intervals for six infusions. Some advocate for moving to a maintenance regimen after

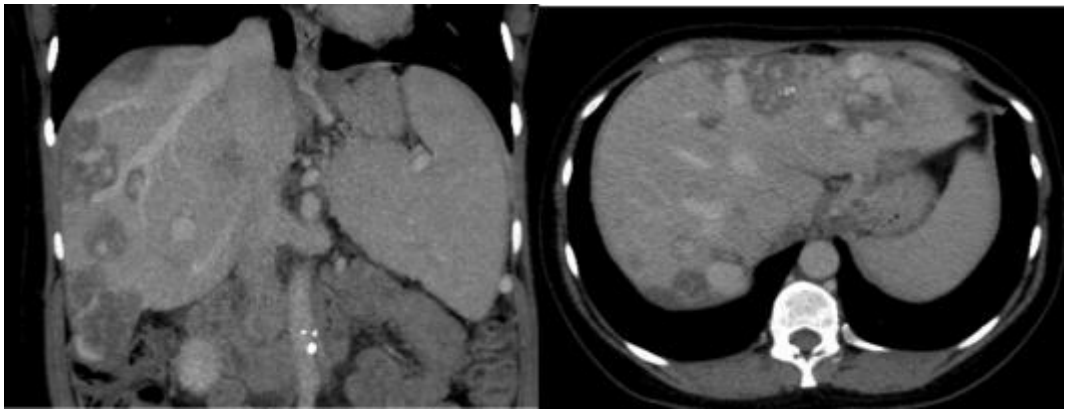

FIGURE 12 Examples of hypo attenuated lesions in coronal and axial views respectively of the same patient with HHT.

three infusions if sufficient clinical response is seen.[61] Maintenance dosing is variable, and tends to be tailored to the patients' response and any complications of therapy.[61]

The data for the use of bevacizumab is limited to small numbers of patients, principally given the rare nature of HHT. Its role is not certain, particularly optimal dosing regimens and its role in potential liver transplant patients. Caution should be exercised where patients have thrombocytopenia and especially where oesophageal varices may be present.

Although bevacizumab is well tolerated in HHT, side effects do occur and may influence patient selection for this therapy. It is recommended the patients on bevacizumab have blood pressure, blood chemistry and urine protein monitoring.[43,55,62,63] Data suggest disease manifestations can return if bevacizumab is discontinued so maintenance treatment is recommended but no standard protocol exists.[55,60,64]

Embolisation of hepatic VMs has previously been attempted given its success in treating pulmonary AVMs but has significant complications such as hepatic or biliary necrosis, cholangitis and had a mortality risk and thus is not recommended.[24,65]

6.3 | Liver transplantation

Liver transplantation (LT) is the only potentially curative option for those patients with symptoms from hepatic VMs (including high-output cardiac failure) that do not respond to intensive medical management.[26,30,66–71] Referral for consideration of LT for patients with symptomatic complications of liver VMs specifically refractory HOCF, biliary ischaemia or portal hypertension should be considered. Liver VMs in HHT are not associated with liver insufficiency, and are included in MELD (Model for End Stage Liver Disease) exceptions[72]; a MELD score for liver involvement in HHT has been proposed with a score of 22 for intractable HOCF/PH, and 40 for ischemic biliary necrosis.[73] Insofar priority for patients with liver VMs requiring LT should be assessed with experts of HHT.[72] Outcomes after LT in hepatic HHT are favourable, with good 5-year and 10-year survival (92%–82%).[66,68] Asymptomatic rare and late recurrence of liver VMs post transplantation has been reported (8 from 40 patients at a median time of 127 months post-transplant).[74]

The timing of listing for liver transplantation can be challenging, requiring a balance between the potential morbidity and mortality rates associated with liver transplantation as well as the potential for progressive complications of HHT affecting candidacy for LT. The decision to list for LT should be supported by predictors of outcomes namely stage 4 liver VMs at baseline, HHT2 genotype, age at presentation more than 47 years, female gender, haemoglobin level at presentation <8 g/dL and alkaline phosphatase level at presentation >300 UI/L.[31,44] Additional features suggestive of poorer prognosis include the presence of biliary ischaemia or sepsis, elevated serum bilirubin, atrial fibrillation and high blood transfusion requirements.[75]

Whilst bevacizumab may be considered a bridge to transplantation,[26,76] it inhibits wound healing and generally it is recommended the treatment is discontinued at least 1 month prior to surgery (2–6 months optimal) whilst minimising time off therapy.[55] This is challenging to achieve for those on the transplant waiting list.

Rates of non- or partial response to bevacizumab and recurrence of symptoms or signs post drug withdrawal make it unsuitable as a replacement for LT but may offer a bridging role and need for transplantation reassessed in light of response.[26,76] However, a major issue with LT is the availability of organs. Therefore, development of novel therapies as a further management strategy are required.

Post liver transplant immunosuppression is centred around calcineurin inhibition. However, mammalian target of rapamycin (mTOR) inhibitors have been suggested due to their role in angiogenesis.[77] There is experience with this class of drug post liver transplantation with an understanding of the risk benefit profile of their introduction.[78] Introduction of sirolimus is often delayed in the early weeks post liver transplantation due to concerns on its effect on wound healing and hepatic artery thrombus risk.

7 | NOVEL THERAPEUTIC OPTIONS

Whilst there are therapies available, particularly with bevacizumab, there is still a need for the development of additional therapies where

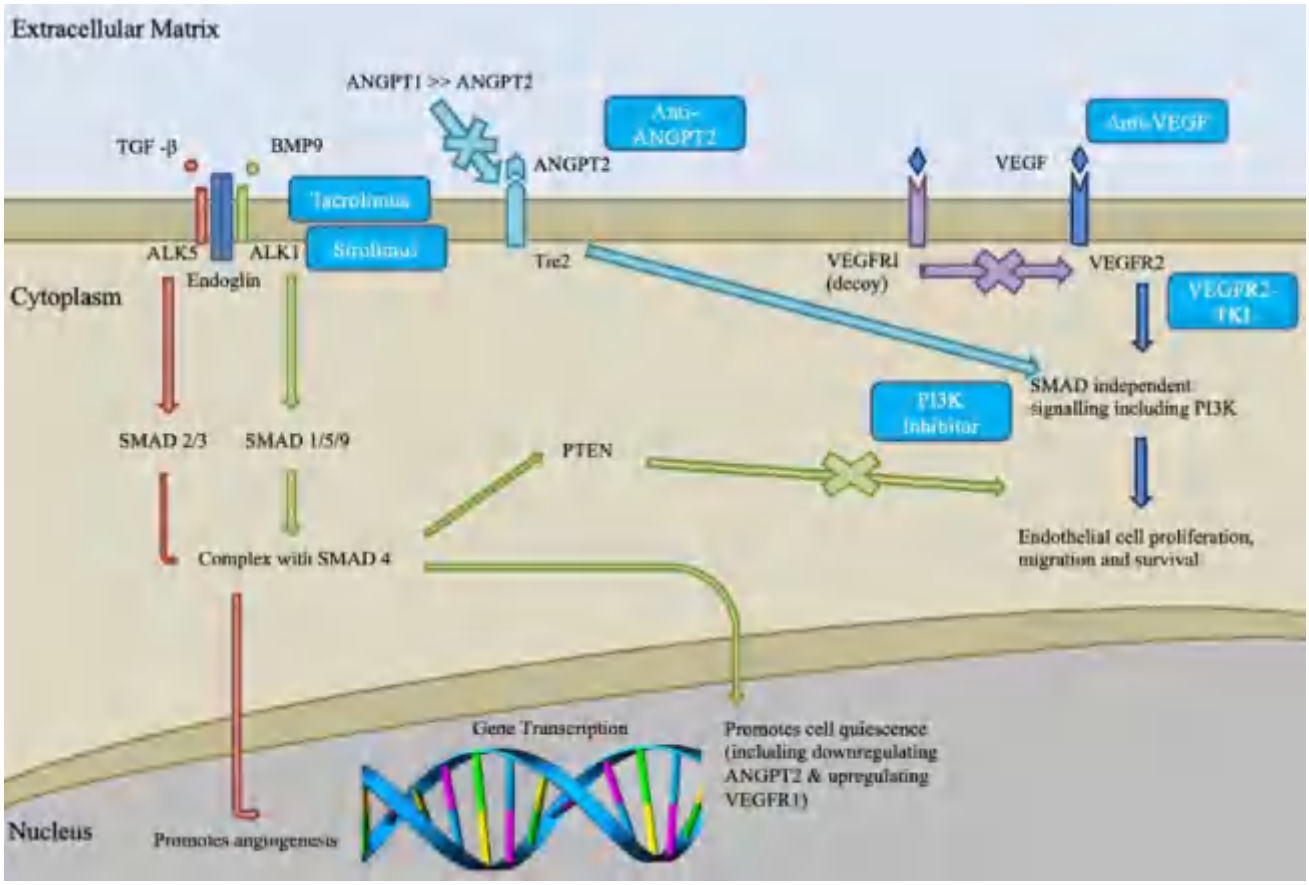

FIGURE 13 Cell signalling pathway outlining the main pathways of both pro- and anti-angiogenic factors that are involved in the pathophysiology of HHT labelled with potential sites for drug targeting labelled. ANGPT2, angiopoietin 2; ALK, activating receptor like kinase; BMP9, bone morphogenetic protein 9; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue; SMAD, mother against decapentaplegic homologue; TGF, transforming growth factor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

bevacizumab is not effective or poorly tolerated. Furthermore, novel therapies which may reverse the abnormal vasculature in HHT could potentially provide a curative option. With this in mind, two drug repositioning methods have been utilised. Firstly, repurposing anti angiogenic drugs used in cancer therapy (anti VEGF antibody, tyrosine kinase inhibitors) in a similar manner to how bevacizumab was discovered could address the imbalance of pro and anti-angiogenic factors that are the hallmark of HHT. Secondly, non-targeted screening of existing drug libraries using an HHT cellular assay could identify previously unrecognised therapeutic targets. Potential action sites for drug therapies in the cell signalling pathway are summarised in Figure 13.

Thalidomide is a drug with both vascular and immunomodulatory effects. Its anti-angiogenic activity may be due to suppression of VEGF, with serum levels of VEGF reduced in patients using thalidomide with gastrointestinal bleeding.[79,80]

Tyrosine kinase inhibitors (TKIs) have antiangiogenic molecules which could also target the VEGF signalling pathway and can be used orally. Sorafenib, a dual RAF kinase/VEGF receptor inhibitor with additional tyrosine kinase targets, and pazopanib and an investigational analogue (multi-target TK inhibitor with anti-VEGF receptor properties) were beneficial in murine models improving anaemia from bleeding in the gastrointestinal tract more than mucocutaneous lesions in the upper aerodigestive tract.[81] A study in humans of pazopanib suggested this drug can reduce bleeding in HHT patients in a proof of concept study.[82] A case study of a patient given Nintedanib which targets the platelet derived growth factor, fibroblast growth factor and VEGF receptors for pulmonary fibrosis who also had HHT noticed a reduction in epistaxis that had bene refractory to other treatments suggesting the use of this drug could be explored further.[83]

Tacrolimus is a calcineurin inhibitor used as an immunosuppressive agent, but may have a role in activating the ALK1-SMAD pathway improving defects caused by ALK1 loss.[84] The mechanism of action in activating this pathway is not understood, but there is potential for this to act directly on the cellular pathological process in HHT. Tacrolimus has also been suggested as a potential treatment for pulmonary arterial hypertension irrespective of HHT.[85] However, a case report of a pulmonary arterial hypertension patient with HHT treated with tacrolimus saw improvement in epistaxis that was previously refractory to therapy but no effect on pulmonary arterial hypertension although tacrolimus in HHT still warrants further investigation.[86]

The mammalian target of rapamycin (mTOR) is over produced, similarly to VEGF in HHT patients.[77] When Sirolimus was given post liver transplant to patients with HHT who had multiple AVMs, telangiectasia, epistaxis and anaemia, they improved.[68,87]

Developments over time in mice models have allowed the investigation of these putative drug therapies. Initially, mice that were null for *ACVR11* or *Eng* did not survive, while heterozygous mice for either gene had a minimal phenotype with normal survival. Thus, conditional knockout mice allow inactivation of *ACVR11* or *Eng* at selective times and cells and provide reproducible models of VMs.[88]

Angiopoietin 2 (ANGPT2) is a potent angiogenic factor acting through the TK receptor, and anti-ANGPT2 antibodies have been tested in animal models of HHT improving AVM formation.[89] Downstream of VEGF and ANGPT2, PI3-kinase is also involved in the cell signalling pathway that is disrupted in HHT. PI3-kinase inhibitors have been efficacious in murine experimental HHT models although there have been no clinical trials as yet.[90,91]

8 | CONCLUSION

HHT is a rare disease of blood vessel formation. Knowledge on the genetic and cell signalling pathways that underpin it have been elucidated in the last two decades. Clinical manifestations are well described with hepatic vascular malformations common; even if symptomatic disease is relatively infrequent at diagnosis, liver VMs entail a non-negligible mortality and morbidity over the follow-up. The commonest clinical manifestation in those patients with liver involvement is high-output cardiac failure. Portal hypertension can also occur either directly from hepatic artery to portal venous shunts or nodular regenerative hyperplasia from an abnormal hepatic blood supply. Biliary complications including biliary ischemia and possibly necrosis are also features.

Bevacizumab, an anti-VEGF monoclonal antibody, is effective in reducing cardiac output in those with liver manifestations of HHT and also other symptoms of this condition including bleeding. Whilst liver transplantation is the only curative option for liver VMs, it is a major surgery. Therefore, novel therapies for HHT patients are desirable, with ongoing research into anti-angiogenic drugs and those which target the aberrant cell signalling pathway being explored but more data are needed.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any disclosures to report.

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REFERENCES

1. Fleagle JM, Bobba RK, Kardinal CG, Freter CE. Iron deficiency anemia related to hereditary hemorrhagic telangiectasia: response to treatment with bevacizumab. *Am J Med Sci*. 2012;343(3):249-251.
2. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet*. 2009;17(7):860-871.
3. McDonald J, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia. *Haematologica*. 2005;90(6):728-732.
4. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-weber syndrome). *Am J Med Genet*. 2000;91(1):66-67.
5. Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet*. 1996;13(2):189-195.
6. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet*. 1994;8(4):345-351.
7. Gallione CJ, Repetto GM, Legius E, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet*. 2004;363(9412):852-859.
8. Gallione CJ, Richards JA, Letteboer TGW, et al. SMAD4 mutations found in unselected HHT patients. *J Med Genet*. 2006;43(10):793-797.
9. Lesca G, Burnichon N, Raux G, et al. Distribution of ENG and ACVRL1 (ALK1) mutations in French HHT patients. *Hum Mutat*. 2006;27(6):598.
10. Balachandar S, Graves TJ, Shimonty A, et al. Identification and validation of a novel pathogenic variant in GDF2 (BMP9) responsible for hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformations. *Am J Med Genet A*. 2022;188(3):959-964.
11. Clarke JM, Alikian M, Xiao S, et al. Low grade mosaicism in hereditary haemorrhagic telangiectasia identified by bidirectional whole genome sequencing reads through the 100,000 genomes project clinical diagnostic pipeline. *J Med Genet*. 2020;57(12):859-862.
12. Bayrak-Toydemir P, McDonald J, Markewitz B, et al. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. *Am J Med Genet A*. 2006;140(5):463-470.
13. Anderson E, Sharma L, Alsafi A, Shovlin CL. Pulmonary arteriovenous malformations may be the only clinical criterion present in genetically confirmed hereditary haemorrhagic telangiectasia. *Thorax*. 2022;77(6):628-630.
14. Kazerounian S, Lawler J. Integration of pro- and anti-angiogenic signals by endothelial cells. *J Cell Commun Signal*. 2018;12(1):171-179.
15. David L, Mallet C, Mazerbourg S, Feige JJ, Bailly S. Identification of BMP9 and BMP10 as functional activators of the orphan activin receptor-like kinase 1 (ALK1) in endothelial cells. *Blood*. 2007;109(5):1953-1961.
16. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature*. 2000;407(6801):249-257.
17. David L, Mallet C, Keramidas M, et al. Bone morphogenetic protein-9 is a circulating vascular quiescence factor. *Circ Res*. 2008;102(8):914-922.
18. Wood JH, Guo J, Morrell NW, Li W. Advances in the molecular regulation of endothelial BMP9 signalling complexes and implications for cardiovascular disease. *Biochem Soc Trans*. 2019;47(3):779-791.
19. Hernandez F, Huether R, Carter L, et al. Mutations in RASA1 and GDF2 identified in patients with clinical features of hereditary hemorrhagic telangiectasia. *Hum Genome Var*. 2015;2:15040.
20. Wooderchak-Donahue WL, McDonald J, O'Fallon B, et al. BMP9 mutations cause a vascular-anomaly syndrome with phenotypic overlap with hereditary hemorrhagic telangiectasia. *Am J Hum Genet*. 2013;93(3):530-537.

21. Hao Q, Su H, Marchuk DA, et al. Increased tissue perfusion promotes capillary dysplasia in the ALK1-deficient mouse brain following VEGF stimulation. *Am J Physiol Heart Circ Physiol*. 2008;295(6):H2250-H2256.
22. Snellings DA, Gallione CJ, Clark DS, Vozoris NT, Faughnan ME, Marchuk DA. Somatic mutations in vascular malformations of hereditary hemorrhagic telangiectasia result in Bi-allelic loss of ENG or ACVRL1. *Am J Hum Genet*. 2019;105(5):894-906.
23. Kritharis A, Al-Samkari H, Kuter DJ. Hereditary hemorrhagic telangiectasia: diagnosis and management from the hematologist's perspective. *Haematologica*. 2018;103(9):1433-1443.
24. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *J Med Genet*. 2011;48(2):73-87.
25. Porteous ME, Burn J, Proctor SJ. Hereditary haemorrhagic telangiectasia: a clinical analysis. *J Med Genet*. 1992;29(8):527-530.
26. Faughnan ME, Mager JJ, Hetts SW, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med*. 2020;173(12):989-1001.
27. Bayrak-Toydemir P, McDonald J, Akarsu N, et al. A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. *Am J Med Genet A*. 2006;140(20):2155-2162.
28. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. Complications and mortality in hereditary hemorrhagic telangiectasia: a population-based study. *Neurology*. 2015;84(18):1886-1893.
29. Buonamico P, Suppressa P, Lenato GM, et al. Liver involvement in a large cohort of patients with hereditary hemorrhagic telangiectasia: echo-color-doppler vs multislice computed tomography study. *J Hepatol*. 2008;48(5):811-820.
30. Buscarini E, Plauchu H, Garcia Tsao G, et al. Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. *Liver Int*. 2006;26(9):1040-1046.
31. Buscarini E, Leandro G, Conte D, et al. Natural history and outcome of hepatic vascular malformations in a large cohort of patients with hereditary hemorrhagic teleangiectasia. *Dig Dis Sci*. 2011;56(7):2166-2178.
32. Lesca G, Olivieri C, Burnichon N, et al. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. *Genet Med*. 2007;9(1):14-22.
33. Buscarini E, Danesino C, Olivieri C, et al. Doppler ultrasonographic grading of hepatic vascular malformations in hereditary hemorrhagic telangiectasia—results of extensive screening. *Ultraschall Med*. 2004;25(5):348-355.
34. Gincul R, Lesca G, Gelas-Dore B, et al. Evaluation of previously nonscreened hereditary hemorrhagic telangiectasia patients shows frequent liver involvement and early cardiac consequences. *Hepatology*. 2008;48(5):1570-1576.
35. Garcia-Tsao G. Liver involvement in hereditary hemorrhagic telangiectasia (HHT). *J Hepatol*. 2007;46(3):499-507.
36. Garcia-Tsao G, Korzenik JR, Young L, et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med*. 2000;343(13):931-936.
37. Buscarini E, Danesino C, Plauchu H, et al. High prevalence of hepatic focal nodular hyperplasia in subjects with hereditary hemorrhagic telangiectasia. *Ultrasound Med Biol*. 2004;30(9):1089-1097.
38. Harwin J, Sugi MD, Hetts SW, Conrad MB, Ohliger MA. The role of liver imaging in hereditary hemorrhagic telangiectasia. *J Clin Med*. 2020;9(11):3750.
39. Lee JH, Lee YS, Kim PN, et al. Osler-weber-Rendu disease presenting with hepatocellular carcinoma: radiologic and genetic findings. *Korean J Hepatol*. 2011;17(4):313-318.
40. Jameson CF. Primary hepatocellular carcinoma in hereditary haemorrhagic telangiectasia: a case report and literature review. *Histopathology*. 1989;15(5):550-552.
41. Morii K, Uematsu R, Yamamoto T, et al. Hepatocellular carcinoma in a patient with hereditary hemorrhagic telangiectasia. *Intern Med*. 2018;57(24):3545-3549.
42. Mitchell A, Adams LA, MacQuillan G, Tibballs J, vanden Driesen R, Delriviere L. Bevacizumab reverses need for liver transplantation in hereditary hemorrhagic telangiectasia. *Liver Transpl*. 2008;14(2):210-213.
43. Dupuis-Girod S, Ginon I, Saurin JC, et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. *JAMA*. 2012;307(9):948-955.
44. Singh S, Swanson KL, Hathcock MA, et al. Identifying the presence of clinically significant hepatic involvement in hereditary haemorrhagic telangiectasia using a simple clinical scoring index. *J Hepatol*. 2014;61(1):124-131.
45. Buscarini E, Buscarini L, Danesino C, et al. Hepatic vascular malformations in hereditary hemorrhagic telangiectasia: doppler sonographic screening in a large family. *J Hepatol*. 1997;26(1):111-118.
46. Cavel A, Bleuzen A, Bertrand P, Patat F, Cottier JP. Comparison between doppler ultrasonography and multiphase multidetector-row computed tomography in the detection of liver involvement in Rendu-Osler disease: an analysis of 62 patients. *Diagn Interv Imaging*. 2016;97(4):451-459.
47. Scardapane A, Stabile Ianora A, Sabbà C, et al. Dynamic 4D MR angiography versus multislice CT angiography in the evaluation of vascular hepatic involvement in hereditary haemorrhagic telangiectasia. *Radiol Med*. 2012;117(1):29-45.
48. Milot L, Kamaoui I, Gautier G, Pilleul F. Hereditary-hemorrhagic telangiectasia: one-step magnetic resonance examination in evaluation of liver involvement. *Gastroenterol Clin Biol*. 2008;32(8–9):677-685.
49. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol*. 2010;53(3):397-417.
50. Tripathi D, Stanley AJ, Hayes PC, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut*. 2015;64(11):1680-1704.
51. Felli E, Addeo P, Faitot F, Nappo G, Oncioiu C, Bachellier P. Liver transplantation for hereditary hemorrhagic telangiectasia: a systematic review. *HPB (Oxford)*. 2017;19(7):567-572.
52. Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S. The impact of bevacizumab (Avastin) on survival in metastatic solid tumors—a meta-analysis and systematic review. *PLoS One*. 2013;8(1):e51780.
53. Carmeliet P. Angiogenesis in life, disease and medicine. *Nature*. 2005;438(7070):932-936.
54. Flieger D, Hainke S, Fischbach W. Dramatic improvement in hereditary hemorrhagic telangiectasia after treatment with the vascular endothelial growth factor (VEGF) antagonist bevacizumab. *Ann Hematol*. 2006;85(9):631-632.
55. Guilhem A, Fargeton AE, Simon AC, et al. Intra-venous bevacizumab in hereditary hemorrhagic telangiectasia (HHT): a retrospective study of 46 patients. *PLoS One*. 2017;12(11):e0188943.
56. Al-Samkari H, Kasthuri RS, Parambil JG, et al. An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-bleed study. *Haematologica*. 2020;106(8):2161-2169.
57. Buscarini E, Botella LM, Geisthoff U, et al. Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia. *Orphanet J Rare Dis*. 2019;14(1):28.
58. Epperla N, Hocking W. Blessing for the bleeder: bevacizumab in hereditary hemorrhagic telangiectasia. *Clin Med Res*. 2015;13(1):32-35.
59. Follner S, Ibe M, Schreiber J. Bevacizumab treatment in hereditary hemorrhagic teleangiectasia. *Eur J Clin Pharmacol*. 2012;68(12):1685-1686.

60. Iyer VN, Apala DR, Pannu BS, et al. Intravenous bevacizumab for refractory hereditary hemorrhagic telangiectasia-related epistaxis and gastrointestinal bleeding. *Mayo Clin Proc*. 2018;93(2):155-166.
61. Dupuis-Girod S, Shovlin CL, Kjeldsen AD, et al. European reference network for rare vascular diseases (VASCERN): when and how to use intravenous bevacizumab in hereditary Haemorrhagic telangiectasia (HHT)? *Eur J Med Genet*. 2022;65(10):104575.
62. Kanellopoulou T, Alexopoulou A. Bevacizumab in the treatment of hereditary hemorrhagic telangiectasia. *Expert Opin Biol Ther*. 2013;13(9):1315-1323.
63. Maestraggi Q, Bouattour M, Toquet S, et al. Bevacizumab to treat cholangiopathy in hereditary hemorrhagic telangiectasia: be cautious: a case report. *Medicine (Baltimore)*. 2015;94(46):e1966.
64. Al-Samkari H. Systemic bevacizumab for hereditary hemorrhagic telangiectasia: considerations from observational studies. *Otolaryngol Head Neck Surg*. 2019;160(2):368.
65. Garg N, Khunger M, Gupta A, Kumar N. Optimal management of hereditary hemorrhagic telangiectasia. *J Blood Med*. 2014;5:191-206.
66. Lerut J, Orlando G, Adam R, et al. Liver transplantation for hereditary hemorrhagic telangiectasia: report of the European liver transplant registry. *Ann Surg*. 2006;244(6):854-864.
67. Lee M, Sze DY, Bonham CA, Daugherty TJ. Hepatic arteriovenous malformations from hereditary hemorrhagic telangiectasia: treatment with liver transplantation. *Dig Dis Sci*. 2010;55(11):3059-3062.
68. Dupuis-Girod S, Chesnais AL, Ginon I, et al. Long-term outcome of patients with hereditary hemorrhagic telangiectasia and severe hepatic involvement after orthotopic liver transplantation: a single-center study. *Liver Transpl*. 2010;16(3):340-347.
69. Chavan A, Schumann-Binarsch S, Luthe L, et al. Systemic therapy with bevacizumab in patients with hereditary hemorrhagic telangiectasia (HHT). *Vasa*. 2013;42(2):106-110.
70. Bauer T, Britton P, Lomas D, Wight DGD, Friend PJ, Alexander GJM. Liver transplantation for hepatic arteriovenous malformation in hereditary haemorrhagic telangiectasia. *J Hepatol*. 1995;22(5):586-590.
71. Boillot O, Bianco F, Viale JP, et al. Liver transplantation resolves the hyperdynamic circulation in hereditary hemorrhagic telangiectasia with hepatic involvement. *Gastroenterology*. 1999;116(1):187-192.
72. European Association for the Study of the Liver. EASL clinical practice guidelines: vascular diseases of the liver. *J Hepatol*. 2016;64(1):179-202.
73. Garcia-Tsao G, Gish RG, Punch J. Model for end-stage liver disease (MELD) exception for hereditary hemorrhagic telangiectasia. *Liver Transpl*. 2006;12(12 Suppl 3):S108-S109.
74. Dumortier J, Dupuis-Girod S, Valette PJ, et al. Recurrence of hereditary hemorrhagic telangiectasia after liver transplantation: clinical implications and physiopathological insights. *Hepatology*. 2019;69(5):2232-2240.
75. Young LH, Pollak JS, White RI Jr, Ciarleglio MM, Deng y, Garcia-Tsao G. Predictors of death in patients with HHT, liver vascular malformations and symptomatic heart failure. *Hematol Rep*. 2013;5:6.
76. Dupuis-Girod S, Buscarini E. Hereditary hemorrhagic telangiectasia: to transplant or not to transplant? *Liver Int*. 2016;36(12):1741-1744.
77. Ruiz S, Zhao H, Chandakkar P, et al. Correcting Smad1/5/8, mTOR, and VEGFR2 treats pathology in hereditary hemorrhagic telangiectasia models. *J Clin Invest*. 2020;130(2):942-957.
78. Klintmalm GB, Nashan B. The role of mTOR inhibitors in liver transplantation: reviewing the evidence. *J Transp Secur*. 2014;2014:845438.
79. Klepfish A, Berrebi A, Schattner A. Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Intern Med*. 2001;161(5):767.
80. Sabba C, Gallitelli M, Palasciano G. Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med*. 2001;345(12):926.
81. Kim YH, Kim MJ, Choe SW, Sprecher D, Lee YJ, P Oh S. Selective effects of oral antiangiogenic tyrosine kinase inhibitors on an animal model of hereditary hemorrhagic telangiectasia. *J Thromb Haemost*. 2017;15(6):1095-1102.
82. Faughnan ME, Gossage JR, Chakinala MM, et al. Pazopanib may reduce bleeding in hereditary hemorrhagic telangiectasia. *Angiogenesis*. 2019;22(1):145-155.
83. Kovacs-Sipos E, Holzmann D, Scherer T, Soyka MB. Nintedanib as a novel treatment option in hereditary haemorrhagic telangiectasia. *BMJ Case Rep*. 2017;2017:bcr2017219393.
84. Fernandez-Jorge B, Del Pozo Losada J, Paradela S, Martínez-González C, Fonseca E. Treatment of cutaneous and mucosal telangiectases in hereditary hemorrhagic telangiectasia: report of three cases. *J Cosmet Laser Ther*. 2007;9(1):29-33.
85. Spiekerkoetter E, Sung YK, Sudheendra D, et al. Low-dose FK506 (tacrolimus) in end-stage pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2015;192(2):254-257.
86. Sommer N, Droege F, Gamen KE, et al. Treatment with low-dose tacrolimus inhibits bleeding complications in a patient with hereditary hemorrhagic telangiectasia and pulmonary arterial hypertension. *Pulm Circ*. 2019;9(2):2045894018805406.
87. Skaro AI, Marotta PJ, McAlister VC. Regression of cutaneous and gastrointestinal telangiectasia with sirolimus and aspirin in a patient with hereditary hemorrhagic telangiectasia. *Ann Intern Med*. 2006;144(3):226-227.
88. Tual-Chalot S, Oh SP, Arthur HM. Mouse models of hereditary hemorrhagic telangiectasia: recent advances and future challenges. *Front Genet*. 2015;6:25.
89. Crist AM, Zhou X, Garai J, et al. Angiopoietin-2 inhibition rescues arteriovenous malformation in a Smad4 hereditary hemorrhagic telangiectasia mouse model. *Circulation*. 2019;139(17):2049-2063.
90. Alsina-Sanchis E, García-Ibáñez Y, Figueiredo AM, et al. ALK1 loss results in vascular hyperplasia in mice and humans through PI3K activation. *Arterioscler Thromb Vasc Biol*. 2018;38(5):1216-1229.
91. Ola R, Dubrac A, Han J, et al. PI3 kinase inhibition improves vascular malformations in mouse models of hereditary haemorrhagic telangiectasia. *Nat Commun*. 2016;7:13650.

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