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Review

Review of Pharmacological Strategies with Repurposed Drugs for HHT Related Bleeding

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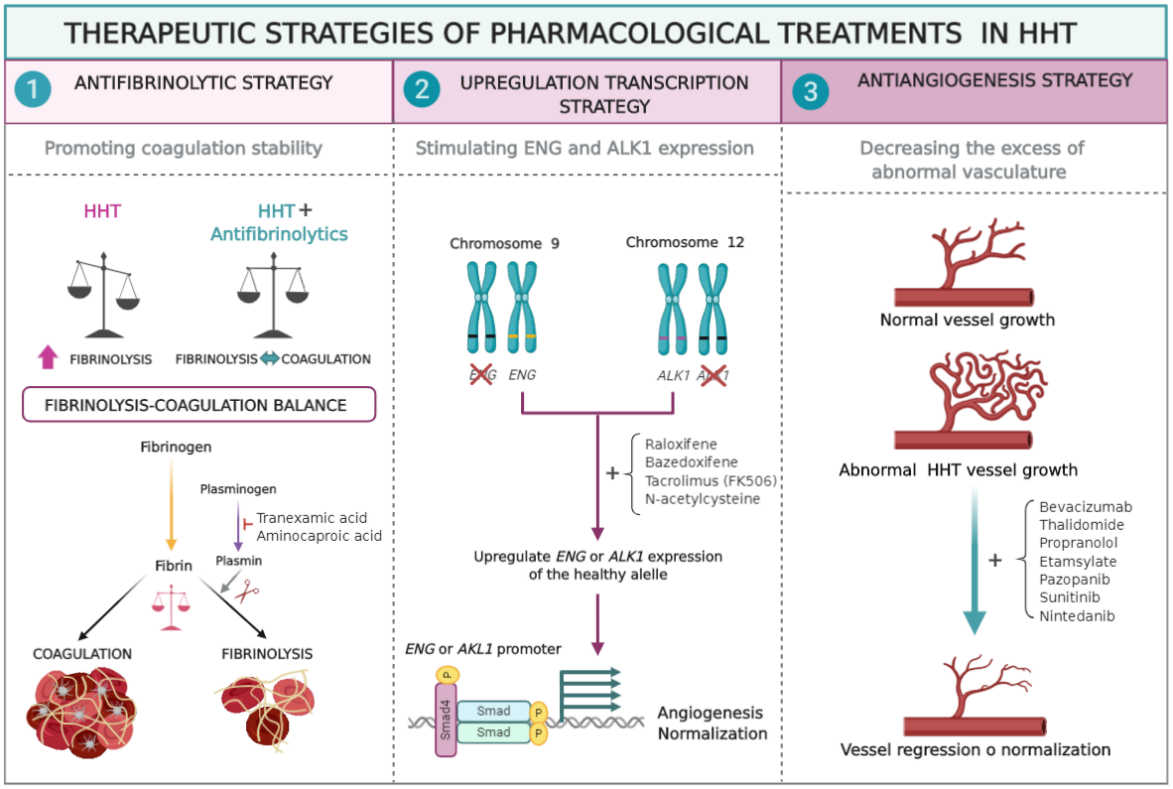
Abstract: Diagnosis of HHT disease is based on the Curaçao criteria: epistaxis, telangiectases, arteriovenous malformations (AVM) in internal organs, and family history. Genetically speaking, more than 90% of HHT patients show mutations in *Endoglin* or *ACVRL1/ALK1* genes, both belonging to the TGF-β/BMP9 signaling pathway. Despite of clearly knowing the symptoms and responsible genes of the disease, we still lack a definite cure for HHT, having just palliative measures and pharmacological trials. Among the former, two strategies: intervention on the "ground zero" balancing the symptoms by iron supplet and blood transfusions to counteract anemia. Among the later, along the last 15 years, three different strategies have been tested: 1) To Favor coagulation with antifibrinolytic agents (Tranexamic acid); 2) To increase transcription of ENG and ALK1 with Specific Estrogen-Receptor Modulators (Bazedoxifene or Raloxifene), antioxidants (N-acetylcysteine, resveratrol), or immunosuppressants (Tacrolimus); and 3) to impair the abnormal angiogenic process with antibodies (Bevacizumab) or blocking drugs like Etamsylate, and Propranolol. This manuscript reviews the main strategies and sum up the clinical trials developed to clarify the different possibilities of the used drugs for alleviating the HHT condition.

Keywords: HHT; ALK1; Endoglin; Raloxifene; Bazedoxifene; Tranexamic acid; Propranolol; FK506; Etamsylate; N-acetyl cysteine



Graphical Abstract: Therapeutic strategies of pharmacological treatments in HHT.

1. Introduction

Hereditary haemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome is a genetic dominant autosomal multisystemic vascular disease, whose penetrance increases with age. The Curacao criteria were designed to diagnose HHT, and include its clinical symptoms which are spontaneous and recurrent epistaxis (nose bleeds), mucocutaneous and gastrointestinal (GI) telangiectases, internal arteriovenous malformations (AVM) mainly in lung, brain or liver and family history (Figure 1A) [1–3]. The prevalence of HHT varies between 1:5000 and 1:8000 on average, although due to the "founder effect" and "insulation effect", the prevalence is higher in some regions such as the Jura region in France, Funen Island in Denmark and the Caribbean Dutch Antilles [3–5]. Heterozygous mutations in either *ENG* or *ACVRL1/ALK1* genes trigger the pathogenesis of HHT in over 90% of HHT patients [6,7]. Less common mutations responsible ~~of~~ 2% of HHT cases, appear ~~on~~ the *MADH4* gene, leading to a combined syndrome of Juvenile Polyposis HHT (JPHT) [8] consisting on HHT symptoms, colon polyps and thoracic aneurysms [9]. Furthermore, chromosomes 5 and 7 have been described to possess two *loci* with unknown genes, that cause HHT3 [10]and HHT4, respectively [11]. An HHT-like syndrome called HHT5 has been linked to mutations in *BMP9*[12]. All mutations leading to HHT are found in genes belonging to the family of BMP9/TGF-β signalling pathway (Figure 1B).

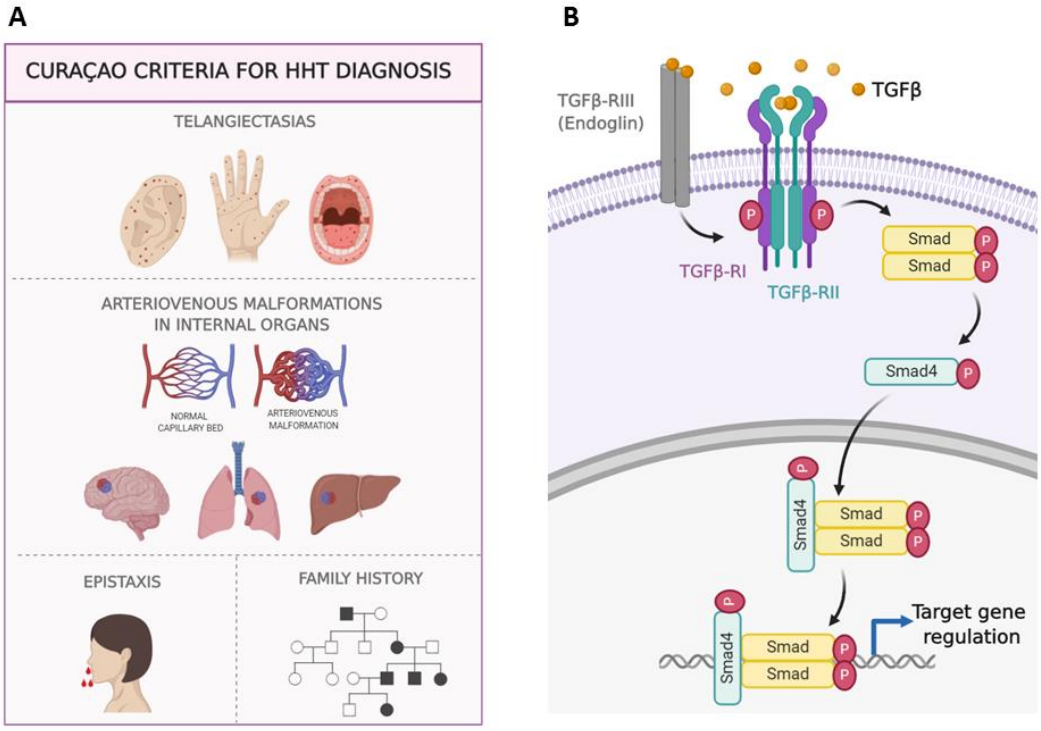


Figure 1

Figure 1. Hereditary Haemorrhagic Telangiectasia.A. Clinical manifestations of HHT, Curaçao criteria. Telangiectases in ear, hands, tongue and lips; arteriovenous malformations in brain, lung, and liver, epistaxis and family history.**B.** TGF-β signalling pathway in endothelial cells. Once ligand binds to its receptor complex (RI, RII, and endoglin,that activates RI phosphorylation), the phosphorylation of TGF-β RI is promoted, leading to the Smads phosphorylation, the translocation of this protein complex to the nucleus and the transcriptional effects on target genes.

Moreover, Capillary ~~m~~alformation/Arteriovenous ~~m~~alformation CM/AVM syndrome is ~~also~~ phenotypically similar to HHT, having as differential diagnosis the appearance of multiple CMs that are small and red, round to oval shaped ~~and~~ with a peripheral white halo ~~at~~ random distribut~~ion.~~ These are linked to heterozygous pathogenic variants in *EPHB4* or *RASA1* identified by molecular genetic testing[13].

This review will focus on the pharmacological treatment for bleeding in HHT patients. With 93% of patients suffering light to moderate bleedings, epistaxis presents as the most frequent clinical manifestation of HHT [14,15]. It affects over 90% of patients before the age of 21, normally interfering with their quality of life [16].Epistaxis are due to the telangiectases of the nasal mucosa, focally dilated venules, often connected directly with dilated arterioles [17]. Directly related to epistaxis is GI bleeding, due to telangiectases on the digestive mucosa and observed in up to 80% of HHT patients [18]. However, GI bleeding becomes more frequent with age[19]. Although currently there is no optimal available treatment for either epistaxis or GI bleeding, the systemic pharmacological treatments that are used for epistaxis might also be useful to manage GI bleedings.

The pharmaceutical therapies which will be commented in the following sections are addressed to the whole organism of an HHT patient, heterozygous for the mutated gene in most of his cells. The therapies mentioned are not addressing the fact that in some cutaneous telangiectases, ECs may be homozygous mutants for *ALK1*/*ENG* according to a recent publication of Snellings *et al*. [20].

2. General care and control of anaemia

To prevent crusting and allow the nasal mucosa to be correctly hydrated in HHT patients, local moisturizing treatments such as humidification, nasal cleaning with a saline solution and lipid-based topical ointments are used[18].Despite these options, it is challenging to completely avoid nasal or GI bleeding in HHT, often leading to iron deficiency and anaemia in these patients. For this reason, the first line of treatment of HHT is focused on managing the anaemia resulting from bleedings. Iron-enriched diets and iron supplements are cost-effective steps that significantly reduce the need of blood. Iron transfusions are necessary in severely affected patients[2,21].

3. Therapeutic Pathways/Strategies of Pharmacological treatments for HHT

The following section will focus on reviewing the pharmacological treatments, from a preclinical perspective. Robert *et al.* have also recently reviewed this topic [22].

Options to control nose and GI bleeding could be used, according to the following strategies(Table 1). It should be commented that the drugs were included into each group, according to the main mechanism observed *in vitro* and/or *in vivo* experiments, yet in some cases other additional mechanisms maybe contributing to the therapeutic effect.

Table 1. Therapeutic strategies to decrease epistaxis in HHT

1	Decrease haemorrhages stabilizing the fibrin network with antifibrinolytics ➢ Tranexamic Acid (TA) ➢ Ε-Aminocaproicacid (AC)
2	Stimulate *ENG* and *ALK1* transcription to increase protein expression to partially overcome haploinsufficiency ➢ SERMs: Raloxifene, Bazedoxifene ➢ Tacrolimus
3	Decrease the abnormal excessive vasculature of the nose mucosa through antiangiogenesis ➢ By inactivating the VEGF signalling pathway • Bevacizumab, Propranolol, Timolol, ThalidomideorPazopanib ➢ By blocking the FGF-R signalling pathway • Etamsylate

- Strategy 1. Despite HHT does not result from a clotting failure, the use of antifibrinolytics to restore the balance between coagulation versus fibrinolysis would help to promote a quicker coagulation and to stabilize the fibrin network Among the antifibrinolytics used for epistaxis treatment, stand out Tranexamicacid (TA) and Ε-Aminocaproicacid (AC)[23,24].

- Strategy 2. HHT disease is mainly caused in most cases by the haploinsufficiency in *ENG* and *ALK1* genes, therefore their protein expression stimulation should revert the HHT disease phenotype. At this point, Raloxifene hydrochloride and Bazedoxifene acetate, two Specific Estrogen Receptor Modulators (SERMs), have proven efficiency and safety, been designated as orphan drugs for HHT (2010 EU/3/10/730 and 2014 EU/3/14/1367; respectively) [25,26].

-Strategy 3. Antiangiogenic therapies tackle the excess of abnormal vasculature present on the nasal mucosa. Therefore, Bevacizumab (BZ), a humanized monoclonal antibody against the main angiogenic factor, the Vascular Endothelial Growth Factor (VEGF), has been widely used and tested

on HHT disease. Its systemic administration has improved hepatic function, delaying the liver transplant [27] but it has not shown conclusive results when tested to decrease epistaxis events by topical spray administration [28,29].

Following the same antiangiogenic strategy,pazopanib, thalidomide, and more recently pomalidomide, have been used inhibiting VEGF pathway.

Alike, other antiangiogenic drugs as Propranolol and Timolol(non-specific β-blockers) have shown their benefits in nose bleeding when administered topically (both) and systemically (Propranolol) [30]in HHT patients. Recently, the use of the Fibroblast Growth Factor receptor (FGFR) blocker Etamsylate, by local spray administration has been proven effective, been designated as orphan drug for HHTin 2018 (EU/3/18/2087) [31].

Table 2 summarizes the clinical trials conducted in HHT with the different drugs, most of them mentioned in this review. In addition, some other recent candidates like Vitamin D, Itraconazole and Doxycyclin are on ongoing clinical trials.

All the above-mentioned drugs used were repurposed medicines, which have the added value of an immediate use in clinical trials since their safety is already confirmed from their first indication. As stated by Masoudi *et al.* (2020)[32],"Drug repurposing is a powerful strategy in the discovery scope because of the time and cost savings". Furthermore, it is an appropriate method for finding therapies for orphan and rare diseases.

3.1. Strategy 1. Antifibrinolysis: Ɛ-Aminocaproic and Tranexamic acids

Antifibrinolytics block the plasminogen to plasmin conversion by inhibition of its enzymatic disaggregation and consequently, stabilization of the fibrin clot. Thus, their rationale use targets the wall of the telangiectases where the fibrinolysis is activated[33,34].

TA and AC are antifibrinolytic agents used for HHT epistaxis. Both may be administered topically (embedding a gauze with the agent) or systemically by oral intake (500 mg/8h or even up to 2 g/day) or intravenous administration. To mention, AC was the first antifibrinolytic used and showed thrombosis as side effect being not recommended in patients prone to thrombosis [35–38]. In addition, TA have shown longer half-life and higher potency (10-fold) than AC [23,24].

In addition to several case reports with successful results, a study with a total of 14 patients without risk of thrombosis and which quality of life was worsened due to epistaxis were selected to take TA (500 mg/8 hours) orally. TA treatment showed that all the patients decreased the nose bleedings and increased their levels of haemoglobin, almost avoiding the transfusion necessity, indicating an overall improvement and no side effects of TA treatment [24]. Despite of the study was not a formal clinical trial; TA was safe and effective at the doses applied. To highlight, TA administered up to 3 g/day was successful to control a massive and life-threatening haemorrhage in an HHT patient [23]. Moreover, some published data from *in vitro* experiments demonstrate on ECs that TA led to increased mRNA and protein levels of ENG and ALK-1, and improved endothelial functions as tubulogenesis and migration [24]. Thus, this mechanism may be also acting concomitantly to the main antifibrinolytic action, although the proposed mechanism is only based on *in vitro* evidence.

Nevertheless, some concern mustbe taken in HHT patients with the elevated levels of the coagulation protein Factor VIII (FVIII) and Factor V Leiden, since some reports show an HHT-related increment of these protein levels that favour thrombotic risk in these patients. Another putative risk factor is the presence of high levels of Factor V Leiden. Therefore, personalized risk-benefit considerations are demanded for HHT management [39].

Finally, two clinical trials were performed in HHT centres to assess the benefits of TA in HHT patients with reports published in 2014. In the French ATERO assay, TA was shown effective in a multinational centre study [40], while Geisthoff *et al.*[41],demonstrated in a double-blind clinical trial phase III-B, the efficiency. However, while TA has demonstrated efficiency by systemic use, when topically used by a nasal spray, it did not significantly decrease nose bleeds when compared to placebo (NOSE study) conducted by the Cure HHT patient in 2016 [28].

Table 2. Compilation of the HHT disease interventional clinical trials

EudraCT/NCT/ACTRN	Country	Phase	Title	Intervention	Outcome	Start Date	Status	Results
NCT00004327	US	2	Phase II Pilot Study of Octreotide, a SomatostatinOctapeptide Analog, for Gastrointestinal Hemorrhage in Hormone-Refractory HHT and Senile Ectasia	Octreotide	-	1995	C	-
NCT00004654	US	3	Phase III Randomized, Placebo-Controlled, Crossover Study of Soy Protein Isolate for HHT	Soy protein	-	1996	C	-
NCT01031992	GE	3	Tranexamic Acid and Epistaxis in HHT	Tranexamic acid	Change of hemoglobin level	2002	C	Article [40]
NCT00375622	IL	2	Anti-Estrogen Therapy for HHT A Double-Blind Placebo-Controlled Clinical Trial	Tamoxifen	Frequency of epistaxis	2005	C	Article [41]
NCT00355108	FR	3	ATERO: A Randomised Study with Tranexamic Acid in Epistaxis of Rendu Osler Syndrome	Tranexamic acid	Average monthly duration of epistaxis	2006	C	Article [42]
NCT00389935	US	2	Thalidomide Reduces Arteriovenous Malformation Related GI	Thalidomide	Blood Transfusion requirements	2006	C	-
NCT00588146	US	2	Phase 2 Study of PEG-Intron in HHT	Pegylated IFN-α2B	Change in Hemoglobin	2007	T	Trial file
EudraCT 2010-020545-26	IT	2	Bevacizumab, an anti-angiogenic monoclonal antibody effective for prevention of hemorrhaging in patients with HHT: possible regression of visceral AVM	Bevacizumab	Frequency of Epistaxis	2008	O	-
NCT01397695	US	2	Topical Bevacizumab for the Management of Recurrent Epistaxis in Patients with HHT	Bevacizumab	ESS, Hematocrit, Hemoglobin and Serum Ferritin Levels	2009	C	Trial file
EudraCT 2008-006755-44	FR	2	METAFORE: Maladie de Rendu-Osler: Etude de l'Efficacité et de la tolérance du Bevacizumabutilisépour le traitement des formes hépatiquessévères. Etude de phase II	Bevacizumab	Effect on cardiac output in patients with severe liver damage	2009	O	-
NCT01402531	US	2	SubmucosalBevacizumab for the Management of Recurrent Epistaxis in Patients with HHT	Bevacizumab	Epistaxis Using the ESS, Hematocrit, Hemoglobin and Serum Ferritin Levels	2010	C	Trial file
EudraCT 2009-018049-19	AT	2	A randomized double blind placebo controlled trial of intranasal submucosalbevacizumab in hereditary hemorrhagic telangiectasia	Bevacizumab	Reduction in average VAS scores of epistaxis	2010	C	-
NCT01408030	US	2	North American Study of Epistaxis in HHT (NOSE)	BevacizumabTranexamic Acid Estriol	Frequency of Epistaxis	2011	C	Article [28]
NCT01408732	US	1	Office-sclerotherapy for Epistaxis Due to HHT	Sclerotherapy with sodium tetradecyl sulfate	Severity of Epistaxis	2011	C	Trial file
NCT01485224	IT	2	Efficacy of Thalidomide in the Treatment of HHT	Thalidomide	Percentage of patients showing a	2011	C	Article

					decrease in the frequency, intensity and duration of epistaxis and in the blood transfusion requirement			[43]
NCT01314274	AT	2	Intranasal SubmucosalBevacizumab for Epistaxis in HHT	Bevacizumab	Relative change in average daily Epistaxis VAS scores compared to baseline	2011	C	Article [44]
NCT01507480	FR	1	The ELLIPSE Study: A Phase-1 Study Evaluating the Tolerance of Bevacizumab Nasal Spray to Treat Epistaxis in HHT	Bevacizumab	Tolerance	2011	C	Article [45]
EudraCT 2011-004096-36	IT	2	Efficacy of thalidomide in the treatment of severe recurrent epistaxis in HHT	Thalidomide	Severity of Epistaxis	2011	C	-
NCT01908543	UK	NA	Iron Deficiency and HHT	Ferrous sulphate	Blood iron indices	2013	T	Article [46]
NCT01752049	CA	NA	Topical Anti-angiogenic Therapy for Telangiectasia in HHT: Proof of Concept	Timolol maleate	Mean reduction in lesion area (compared with baseline measurement) of treated telangiectasia	2013	C	-
NCT02389959	US	4	Intranasal Bevacizumab for HHT-Related Epistaxis	Bevacizumab	Improvement in ESS	2014	R	-
EudraCT 2013-004204-19 & NCT02157987	FR	1-2	Treatment of HHT of the Nasal Mucosa by Intranasal Bevacizumab: Search for Effective Dose	Bevacizumab	Decrease of at least 50% of number of epistaxis in a month compared to the month before inclusion	2014	C	-
NCT02638012	CA	NA	Prospective Pilot Study of Floseal for the Treatment of Anterior Epistaxis in Patients With HHT	Floseal	Change in ESS	2015	C	Article [47]
NCT02204371	US & CA	2	Evaluation of Pazopanib on Bleeding in Subjects with HHT	Pazopanib	Change from Baseline in ESS at the Indicated Time Points	2015	T	Trial file
NCT02287558	US	1	Pomalidomide in HHT and Transfusion-Dependent Vascular Ectasia: a Phase I Study	Pomalidomide	Transfusion requirement measure	2015	R	-
EudraCT 2015-000385-55 & NCT02484716	FR	2	Efficacy of a Timolol Nasal Spray as a Treatment for Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT) - (TEMPO)	Timolol	Efficacy of timolol nasal spray on duration of nosebleeds for 3 months after the end of the treatment	2015	C	Article [48]
EudraCT 2016-003982-24	ES	4-2	A phase IV-II, single-center, open, single arm treatment, low level of intervention, to assess the efficacy clinical trial and safety of intranasal administration of ethamsylate in the treatment of HHT, during 4 weeks	Ethamsylate	Frequency of epistaxis	2016	C	Article [31]
EudraCT 2016-001340-19 & NCT02874326	NE	2	Octreotide in Patients with GI Bleeding Due to Rendu-Osler-Weber	Octreotide LAR	No endoscopy and no blood/iron transfusions during treatment period	2016	C	Article [49]

NCT04167085	US	4	NOrth American Study for the Treatment of Recurrent epIstaxis With DoxycycLine: The NOSTRIL Trial	Doxycycline	Frequency of epistaxis	2017	O	-
NCT02963129	AR	3	Treatment of Nasal Staphylococcus Aureus Colonization in Patients With HHT	Mupirocin	Nosebleed by Sadick scale	2017	U	-
NCT03981562	CA	2	Vitamin D and HHT	Vit D	Change in ESS	2018	R	-
EudraCT2017-003272-31	NL	2	Efficacy and safety of oral itraconazole in the reduction of epistaxis severity in HHT	Itraconazole	Change in epistaxis severity	2018	O	-
NCT03397004	CA	2	Doxycycline for HHT	Doxycycline Hyclate	Reduction in epistaxis (nose bleeding) severity over 96 weeks	2018	R	-
NCT04113187	FR	3	Propranolol for Epistaxis in HHT a Patients	Propranolol	Cumulative duration of epistaxis (in minutes)	2019	Not R	-
NCT04139018	US	2	Timolol Gel for Epistaxis in HHT	Timolol Gel	Epistaxis Severity Scale	2019	Not R	-
NCT03910244	US	2	Pomalidomide for the Treatment of Bleeding in HHT	Pomalidomide	Change in ESS	2019	R	-
NCT03850730	US	1-2	Pazopanib for the Treatment of Epistaxis in HHT	Pazopanib	Percent change in epistaxis duration in minutes	2019	Not R	-
NCT03850964	US	2-3	Pazopanib Effects on Bleeding in HHT	Pazopanib	Change in epistaxis duration in minutes	2019	Not R	-
EudraCT 2019-003585-40	NL	NA	An uncontrolled, open label pilot-study assessing the efficacy in reducing bleeding severity, and the safety of oral tacrolimus in patients with HHT	Tacrolimus	Change in the epistaxis and/or gastrointestinal severity	2019	O	-
EudraCT 2019-002593-31	FR	2	Efficacy of Nintedanib as a treatment for epistaxis in HHT disease. A national, randomized, multicenter phase II study EPICURE	Nintedanib	Frequency of Epistaxis	2019	O	-
EudraCT 2018-004179-11	NL	2	Effectiveness of Somatostatin Analogues in Patients with HHT and symptomatic GI, the SAIPAN-trial: a multicenter, randomized, open-label, parallel group, superiority trial	Somatostatin Analogues	Decreasing the transfusion requirements	2019	O	-
ACTRN12619001020178	AU	2	A pilot study assessing the effectiveness of oral Propranolol in preventing epistasis in patients with HHT	Propranolol	Change in Epistasis	2019	Not R	-
NCT03954782	FR	2	Efficacy of Nintedanib as a Treatment for Epistaxis in HHT Disease	Nintedanib	Epistaxis duration	2020	O	-

Table 2. Compilation of the HHT disease interventional clinical trials registered at the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu), the U.S. National Library of Medicine (https://clinicaltrials.gov), and the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/Default.aspx). Only interventional trials where a therapeutic drug is tested are listed.

Abbreviations: Countries: AR (Argentina); AT (Austria); AU (Australia); CA (Canada); ES (Spain); FR (France); IL (Israel); IT (Italy); NL (Netherlands); UK (United Kingdom); US (United States of America). Phase: NA (Not Applicable). Status: C (Completed); R (Recruiting); O (Ongoing); T (Terminated); U (Unknown).

3.2. Strategy 2. Upregulating ENG and ACVRL1

3.2.1. Hormonal Therapy: Specific Estrogen Receptor Modulators (SERMs)

Epistaxis has been observed to be increased in women after they have reached menopausal age, suggesting that estrogens might play a protective role in HHT-derived bleeding in women. Post-menopausal women are also affected by osteoporosis, the imbalance in the rate of bone remodelling/resorption that predisposes the elder to higher chances of bone fracture. NFκB, RANK and its ligand RANKL, as well as osteoprotegerin (OPG) play a major role in this pathogenesis [50] (Figure 2). Based on the observation that pre-menopausal HHT women had fewer epistaxes, a study developed by the Yale University's Vascular Malformation Centre attempted to treat the bleedings of 40 transfusion-dependent HHT patients, with a mean age of 57 years, by means of Estradiol treatment. Men, to avoid estradiol feminizing effects, were also treated with Ethinylestradiol/Norethindrone and Danazol. The results were satisfactory as most of the 40 patients showed an improvement in haemoglobin levels and needed fewer blood transfusions [51].

The use of hormones to treat HHT-induced bleedings was published later in the form of case reports, but mostly without controls[52]. The main conclusion obtained from these studies was that estrogen-progesterone administered at the doses typically used for oral contraception might reduce bleedings in symptomatic HHT women, becoming a reasonable option for fertile HHT female patients. Zacharski *et al*. published in 2001 a case report in which the use of Tamoxifen had ceased epistaxis in the long term in a post-menopausal patient, concluding for the first time that SERM was properly used to treat epistaxis in an HHT patient [53]. According to this, Tamoxifen was used in two clinical trials where it again successfully decreased epistaxis. The first of these two consisted of a placebo controlled clinical trial that included both men and women, while the second comprised a long-term monitored clinical trial in which patients were administered 20 mg Tamoxifen[42,54].

In the line of using SERMs to decrease HHT-related bleedings, the safety and efficiency of Raloxifene hydrochloride was tested. Spanish HHT reference unit IDIVAL (Sierrallana/Valdecilla).Raloxifene hydrochloride shows similarities with Tamoxifen, also presenting beneficial effects on bone mineralization and on prevention of cardiovascular and gynaecological cancer. This study included 19 post-menopausal women, previously diagnosed with osteoporosis, and compared the amount of bleeding before and after 6 months of treatment (no placebo was included in the study).Oral intake of Raloxifene (60 mg/day) showed a significant reduction in both the frequency and the amount of epistaxis after 6 months of treatment, also revealing an increase in haemoglobin levels [25].Raloxifene has been shown to be a transcriptional activator of *ENG* and *ACVRL1/ALK1*promoters, binding to their proximal regions and subsequently increasing these genes' transcription rate in a context of in vitro experiments on ECs [25]. As a consequence, the protein levels of ENG and ALK1increased, thus compensating partially the haploinsufficiency suffered by HHT patients in this study[25]. In 2010, these studies resulted in the EMA and FDA designation of Raloxifene hydrochloride as the first orphan drug to treat bleedings in HHT patients (EU/3/10/730).Bazedoxifene acetate, another SERM, significantly decreased the frequency and intensity of epistaxis, while also improving haemoglobin levels as early as one month after treatment with 20 mg/day[26]. In this case, the increase of ENG and ALK1 was not only observed in experiments in vitro with ECs treated with Bazedoxifene, but also, in vivo, by measuring ENG andALK1 levels in macrophages derived from patients before and after Bazedoxifene treatment. Bazedoxifene was also designed as orphan drug for HHT in 2014 by the EMA(EU/3/14/1367).

Of note, estrogens and SERMs,as hormonal receptor ligands, increase the transcription of different promoters, among them, those of coagulation factor genes. Thus, *ENG* and *ACVRL1*are among the stimulated genes, but are not the only. In relation to this fact, especially when the treatment with SERMs may upregulate coagulation factors' genes, blood tests should be performed periodically to HHT patients under SERM treatment to prevent thrombotic events[55].

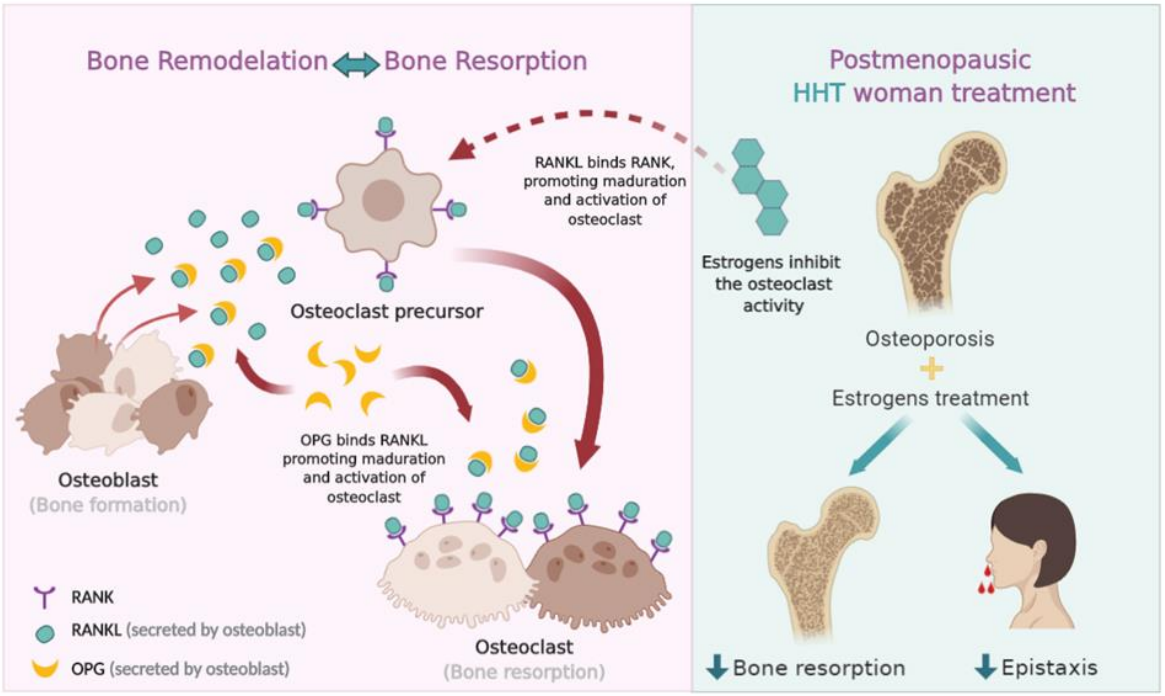


Figure 2. Scheme of Bone formation vs. Bone resorption. Bone remodelling is promoted by the activity of osteoclasts and osteoblasts. RANKL is a protein expressed by osteoblasts which, upon binding to its RANK receptor on the cell surface of osteoclasts and their precursors, causes RANK to stimulate and promote the adhesion of osteoclasts to bone, thus activating their function and preventing apoptosis. OPG is synthesized by the osteoblasts and acts as a decoy receptor, preventing the binding of RANKL to RANK, therefore decreasing the activity of the osteoclast and its survival [50]. For this reason, for years post-menopausal patients with diagnosed osteoporosis have been receiving estrogenic treatment, which, while correcting this imbalance in bone remodelling, also reduces the activity of the osteoclast and activates the expression of OPG This is also capable of reducing the epistaxis of these patients [25,42,51,54].

Finally, Phytoestrogens, compounds of plant origin with structural similarities with the natural estrogen 17β-Estradiol, deserve some words in this section as natural plant estrogen related products. Among them, the isoflavone Genistein and the coumestan Resveratrol are the most relevant in references related to HHT. Genistein is found in numerous plant species such as soy and red clover and Resveratrol in grape skin and in dried fruits ~~such as~~ nuts. These phytoestrogens show high affinity for estrogenic receptors. Genistein and Resveratrol are involved in reducing inflammation, stimulating apoptosis and inhibiting angiogenesis[56,57],and might present therapeutic benefits in HHT patients as natural analogues to SERMs and estrogens.

3.2.2. Immunosuppressor Tacrolimus (FK506)

Albiñana *et al.* reported the efficacy of Tacrolimus (FK506) in increasing ENG and ALK1 expression[58,59]. The reason to test this drug came from a case report of an HHT patient who was administered the immunosuppressor FK506 in low doses, in combination with aspirin and sirolimus to avoid rejection of a liver transplant. One month after he started said treatment, it was observed that his telangiectases (both internal and external), epistaxis and anemia had all been extinguished [60]. Based on this report, cultured ECs were treated with Tacrolimus and an increase on the protein and mRNA expression of ENG and ALK1 and enhancement of the TGF-β1/ALK1 signalling pathway and EC functions like tubulogenesis and cell migration were observed [58,59].These results would explain the improvement in the abovementioned patient, by means of a partial compensation of Endoglin and ALK1 haploinsufficiency. Supporting this view, five years later, Ruiz *et al.* reported

increase ALK-1 signaling pathway in HHT patient-derived endothelial cells. In an HHT animal model, Tacrolimus also inhibited VEGF signaling, decreasing hypervascularization[61].

In a more clinical context, Sommer *et al*. published in 2019 that low doses of FK506/Advagraf decreased bleeding in an HHT patient presenting also pulmonary arterial hypertension[62]. Considering that this is a single case, it is especially interesting since high doses of Tacrolimus (5-10mg/day, normally used for immunosuppression in transplant) cannot be currently administered to treat chronic HHT-bleeding. This case report points to low doses of Tacrolimus (0.5-1.5 mg/day) as the optimal range for patients with nose or GI refractory bleeding [62].An additional report by Hosman *et al*., including 2 patients dependent on HHT transfusions due to severe bleeding, demonstrates improvement after treatment with low-dose Tacrolimus[63]. Currently, and according to the HHT European Federation, around 24 HHT patients are being treated "off label" with low Tacrolimus doses, prescribed by HHT reference doctors, to control epistaxis and GI bleeding.

Finally, the clinical trial named TACRO is addressing the efficacy and safety of 0.1% Tacrolimus topically applied as nasal ointment for epistaxis[64]. At the time this review is written, a total of 50 patients have been randomized and treated and the results are under analysis.

3.2.3. N-acetyl-cysteine

Based on that free O_2-radicals might cause precapillary sphincter abnormalities, resulting in epistaxis, Gussem *et al*. in 2009 wondered whether antioxidants like N-acetyl-cysteine (NAC) could neutralize those free O_2-radicals and reduce or avoid nose bleedings. Thus, 43 patients were followed-up for frequency, severity, and duration of epistaxis after a daily treatment of 600 mg NAC for 12 weeks. The trial concluded that the NAC significantly reduced the nose-bleedings in HHT patients and specifically during the day and in HHT1 male patients[65].

Based on these results, Albiñana *et al.* studied the *in vitro* effects of 100 μM NAC in ECs on ENG and ALK1 expression levels. After 24 hours incubation, although there were no changes on ALK1 levels, mRNA and protein levels of ENG increased up to 2 and 1.5-2 folds, respectively[66]. These data suggest why the HHT1 patients treated as described before, significantly improved their symptoms[65].

3.3. Strategy 3. Antiangiogenesis

Antiangiogenic strategies on HHT act on the mucosa to decrease or normalize its abnormal excessive vasculature. Two key angiogenic pathways in ECs are those triggered by VEGF and FGF.

3.3.1. Anti-VEGF and Tyrosine Kinase Inhibitors (TKI)

VEGFs specifically act on vascular EC and are a key stone in the angiogenic and lymphangiogenic process in both physiological and pathological conditions such as tumours or wound healing[67]. VEGFs play an important role in HHT disease since high protein levels have been reported in HHT patients[68–71].

Bevacizumab (BZ) (Avastin ®), the recombinant humanized monoclonal antibody against VEGF-A ranks the first antiangiogenic therapeutic agent approved for advanced colorectal cancer [72]. Since then, BZ has been widely administered in other pathologies such as non-small cell lung cancer diabetic retinopathy or age-related macular degeneration [73].

The antiangiogenic properties of Avastin were successfully tested in isolated cases of HHT patients. BZ reverted the need for transplantation in a patient with HHT1and recovered a HHT patient from a malignant mesothelioma[74]. It also decreased the transfusion requirements and cardiac output in a patient with GI[75]. Thus, the French HHT Network designed a single centre phase II clinical trial to address the delay in liver transplantation on HHT patients with serious liver complication[27].BZ significantly decreased the cardiac output and reduced episodes of epistaxis. Nevertheless, symptoms did not disappear after withdrawal of the drug, making Avastin unsuitable

as a surrogated alternative for orthotopic liver transplant (OLT) in HHT. These results supported the designation of Bevacizumab as orphan drug for HHT in 2014 (EU/3/14/1390).

It is very difficult to determine the optimum time to perform OLT in severe complicated liver VMs in HHT. OLT is a radical cure for liver VMs, and it should be the therapeutic choice in patients under the age of 65 years due to its excellent outcomes, being BZ a better option for patients over 65, much more susceptible to higher risk derived from surgery [76].

BZ has been also administered for very severe epistaxis. Despite of its good results decreasing epistaxis and GI after intravenous administration, it has also serious side effects. Therefore, in those patients where no other option is available, an individualized BZ treatment should be supplied; since HHT is a chronic disease[27,76,77].This individualized re-dosing strategy will not compromise the patient's safety or quality of life and will significantly reduce the costs [78].

BZ has also been assayed topically as nasal spray for epistaxis. The NOSE assay (under the Cure HHT support in USA, 2011-2015) and the French Ellipse clinical trial (2011-2012) ran in parallel. Unfortunately, no significant improvement could be demonstrated for the BZ *vs.* saline solution spray[28,29].

An alternative therapeutic approach for reducing epistaxis and GI bleeding caused by the over activated VEGF pathway is the blockade of the tyrosine-kinase activity of the VEGF receptor. As a proof of concept, the therapeutic effect of the tyrosine-kinase inhibitor GW771806 (a Pazopanib analogue), was tested in an Alk1-inducible knockout (iKO) murine HHT2 model. The oral administration of GW771806 significantly improved anaemia and GI bleeding in HHT2 mice[79]. Unfortunately, its corresponding phase II human trial, designed to follow-up adult HHT patients with significant epistaxis, anaemia, or with transfusions could not be completed. A prospective, multi-center, open-label, dose-escalating study on Pazopanib has been also published and the results show promising improvements in haemoglobin levels and epistaxis in treated patients[80].

Related to Pazopanib and in a further step, Nintedanib, a tyrosine kinase inhibitor, targeting growth factor receptors involved in angiogenesis: platelet-derived growth factor receptor (PDGFR), FGFR and VEGFR, will be assayed as a therapeutic drug in a clinical trial. Nintedanib treatment in combination with rapamycin, synergizes to completely block the AVMs in HHT mice pre-clinical models[81]. This has been the main rationale to continue with Nintedanib in clinical trials. In that sense, Epicure, a randomized, multicentre, phase II, double-blind placebo-controlled study promoted by the French Hospices Civils de Lyon, has started its recruitment in 2019. Epicure will test the antiangiogenic benefits of the tyrosine kinase inhibitor Nintedanib in epistaxis. Initially, patients will be monitored for 24 weeks: 12-weeks of oral treatment plus 12-weeks of follow-up. Theoretically, Nintedanib, as a non-specific/wide range tyrosine kinase inhibitor should allow a reduction of epistaxis in HHT[82].

Finally, in this section dealing with drugs interfering with the VEGF signalling pathway, Thalidomide deserves special mention, since it has been used for epistaxis and GI bleeding in HHT. Its mechanism of action was published in 2010 [43] and since then, several case reports and clinical trials have been performed (Table 2)prior to its designation as an orphan drug (Table 3). Evidence supporting Thalidomide compares favourably in cases of serious and refractory GI and nosebleeds. However, risk *vs.* benefit should be carefully studied, due to the reported side effects for Thalidomide [77]. A derivative of Thalidomide with potentially fewer side effects, Pomalidomide, has been promoted for a multicentre randomized double-blind placebo controlled clinical trial currently ongoing sponsored by the NIH (Table 2).

3.3.2. Non-selective adrenergic β-blockers (ADRB)

Non-selective adrenergic β-blockers of receptors β1and β2 (ADRB 1 and 2) as the known Propranolol and Timolol, have shown antiangiogenic properties related to vasoconstriction, inhibition of EC migration and proliferation and reduced VEGF expression[30,83–85]. Given that an excessive activation of the VEGF pathway is involved in the development of abnormal telangiectases, the properties of these non-selective adrenergic β-blockers may be useful topically.

Propranolol and Timolol have been used as effective therapies to treat superficial infantile haemangiomas[83–85] and could be considered as a potential treatment option for HHT patients.

The use of topical Timolol has been described in some case reports as well as in clinical trials/studies of HHT. According to several reports, topical Timolol (0.5% ophthalmic solution) improved clearly the frequency and severity of epistaxis [86,87]. Those studies were done in individual patients as well as in bigger groups of HHT patients, with clear positive results in all cases. Even though no secondary adverse effects were observed in these cases, there are some contraindications in its applications which should be kept in mind when prescribing and could cause respiratory and cardiovascular problems. In fact, β-blockers are metabolized in the liver by CYP2D6 and the decrease expression of this enzyme, either by concomitant treatment with CYP2D6 inhibitors or by genetic variants, may lead to strong sinus bradycardia[88, 89]. Timolol has also been proved to be an efficient treatment at lower doses (0.1% ophthalmic solution-timogel) in decreasing the extension and appearance of mucocutaneous telangectases in an HHT clinical study, showing 100% and 75% improvement in HHT2 and HHT1 patients, respectively [90].

Propranolol has also been used topically in gel formulation and systemically in tablets with very promising results, although the last method could have some side effects which must be considered before prescribing.

There are several studies supporting the improvement in HHT patients ~~of~~ Propranolol topical administration. In a pilot study done with 6 patients, in which 1.5% Propranolol gel was applied on the nasal mucosa (0.5 ml/day per nostril) the severity of epistaxis and the number of blood transfusions pre and post-administration were reduced fast and significantly [91]. As continuation of this study, the same group ~~finished recently~~ a double-blind placebo-controlled study to assess the efficacy and safety of topical Propranolol for moderate–severe epistaxis in 24 patients with HHT [92]. The combination of sclerotherapy and the use of Propranolol cream at 0.5% prepared in a hospital pharmacy, was evaluated in a cross-sectional study of 38 HHT patients. This combined therapy significantly reduced the frequency and severity of epistaxis, with an Epistaxis Severity Score (ESS) improvement of 5 points (from 6.9 ± 2.6 at the beginning to 1.9 ± 1.3 after the therapy, $p < 0.05$); and increased the quality of life of these patients (in a 5D scale, from 0.66 ± 0.27 before therapy to 0.93 ± 0.12 after the therapy $p < 0.05$) [93].

On the other hand, systemic uptake of Propranolol has some side effects as bradycardia and hypotension. Therefore, Propranolol could be used in a systemic way only in hypertensive HHT patients, following cardiology surveys. For this reason, a clinical study with oral Propranolol (40-120 mg/day) was done in 7 hypertensive HHT patients. Among them, HHT epistaxis disappeared completely in 5 out of 7, while in the other 2 the bleeding reduction was highly significant [94].

3.3.3. Antiangiogenesis by FGF ligand blocking

The FGF family is considered one of the largest families of polypeptide growth factors. FGFs interact with membrane tyrosine kinase receptors (FGF Receptors, FGFRs) through which they signal and exert their diverse biological functions. FGF-1 and FGF-2 were the first two pure polypeptides discovered among all FGFs and are considered one of the most potent factors promoting angiogenesis[95,96]. Later on, more factors promoting angiogenesis were described. FGFs constitutively cooperate with VEGF promoting the proliferation of EC[97] and inducing angiogenesis [98]. Consequently, FGF inhibition constitutes an alternative to the antiangiogenic effect of VEGF, an interesting new therapeutic approach to treat diseases caused by uncontrolled angiogenesis. Many of the characteristics summarized previously suggest that the inhibition of the FGF signalling pathways could be an appropriate treatment to inhibit the abnormal vascularization of HHT patients[99].

FGF signalling may be inhibited *in vitro* and *in vivo* with chemical compounds. One of these products is the anion dihydroxy benzene sulfonate (2,5,DHBS), also known as Dobesilate. Dobesilate is commercially available as tablets of its calcium and N-ethylene ethanamine salts (Doxium and Dicynone, respectively), or as injectable solution (Dicynone or Etamsylate). Experiments done *in vitro* with primary cultures healthy and HHT derived EC, show that Etamsylate acts as an

antiangiogenic factor, inhibiting wound healing and EC tubulogenesis[31]. A pilot clinical trial (EudraCT: 2016–003982–24) was performed with 12 HHT patients treated with a topical spray of Etamsylate twice a day for 4 weeks. The HHT-ESS and other pertinent parameters were analysed and registered. The significant reduction in the HHT-ESS scale (pre-treatment 4.1 *vs*. post-treatment 2.8), together with the lack of significant side effects, allowed the designation of topical Etamsylate as a new orphan drug for epistaxis in HHT patients in 2018 (EU/3/10/18/2087) [31].

4. Summary and Conclusions

The currently available pharmacological treatments for HHT are summarized on Table 1 according to their mechanism of action. The drugs here included may be used on an individual level; treatment for rare diseases should follow the premises of personalized medicine, relying on the reference doctor expertise. A first line of treatment to avoid epistaxis or GI is to reinforce the speed and stability of coagulation with antifibrinolytics, preferentially TA. The only contraindication applies to patients with risk of thrombosis. Doses vary from 1.5 g/day up to 3g/day in episodes of severe bleeding. In countries where TA is not commercially available, AC should be used instead.

For bleedings interfering with normal life, the best treatment option till the moment in women in fertile age are feminine hormones used for contraception. Women in peri- or post-menopausal age will advantage of SERMs. Although SERMs are primarily used to prevent or treat osteoporosis, they have shown to be effective in HHT compensating partially, the haploinsufficiency present in HHT patients by increasing the protein levels of ENG and ALK1. Raloxifene hydrochloride was designated as orphan drug by the EMA and by the FDA. An important characteristic of his drug is that men may take it without risk of feminizing effects, as known by personal communication of clinicians in several cases. Bazedoxifene acetate was also designated as orphan drug by the EMA but it is not commercialized in US.

Between the list of drugs which increases the expression levels of ENG and ACVRL1/ALK1,Tacrolimus was demonstrated to activate signalling of ENG/ALK1 in ECs. It would be the treatment of choice for immunosuppression in transplanted patients. However, recent case reports have opened the possibility of using systemic Tacrolimus at low, non-immunosuppressive doses, to treat HHT bleeding. Currently, around 25 patients are using the treatment as an "off-label" compassionate treatment and it will be very interesting to know about the outcome of these patients. Other treatment includes NAC which increases the *ENG* RNA and protein levels and can be used as an anti-inflammatory and anti-oxidant drug without any side effects.

The antiangiogenic strategy aimed to reduce bleedings and excessive number of abnormal mucosa vessels is in clinical practice of HHT, using anti-VEGF such as Avastin. Tyrosine kinase inhibitors (Pazopanib, Nintenadib, Sunitinib or Buparlisib) and Thalidomide have also been used or are planned to be used in clinical trials[22,82,100,101](Table 2).

Another group of antiangiogenic drugs comprised the non-selective adrenergic β-blockers like Propranolol and Timolol. These drugs would be preferentially used topically, as creams or gels. They reduce nose bleedings by decreasing and delaying the formation of telangiectases on the mucosa. Propranolol could also be used systemically in the cases of hypertensive patients to normalize blood pressure decreasing bleeding simultaneously.

Finally, as emerging treatments, the orphan drug designation of Etamsylate for topical treatment of epistaxis opens a new perspective. Its easy topical administration using sprays and the possibility of FGF inhibition to treat epistaxis follows the antiangiogenic strategy.

This review has delved into the various strategies and clinical trials in HHT that support them, to study the different options of repurposing drugs capable of improving the condition of this disease.

Table 3. Orphan drugs approved by the EMA for HHT disease

Active Substance	Date	EU-Designated Number	Sponsor	Degree of Evidence Clinical Trial
Etamsylate	11/2018	EU/3/10/18/2087	CSIC, Spain	EudraCT: 2016–003982–24
Thalidomide	02/2017	EU/3/17/1845	PlumeStars, S.R.L., Italy	Several clinical trials Table 2
Bevacizumab	12/2014	EU/3/14/1390	Dupuis-Girod, France	Several clinical trials Table 2
Bacedoxifene	11/2014	EU/3/14/1367	CSIC, Spain	Observational study 5 patients
Raloxifene	06/2010	EU/3/10/730	CSIC, Spain	Observational study 19 patients

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Abbreviations:

AC: Aminocaproic acid
ACVRL1/ALK1: Activin A Receptor Like Type 1
AVM: Arterio-Venous Malformation
BMP9: Bone Morphogenetic Protein 9
BOECs: Blood Outgrowth Endothelial Cells
BZ: Bevacizumab
CM: Capillary Malformation
CYP2D6: Cytochrome P450 2D6
ECs: Endothelial Cells
EMA: European Medicine Agency
ENG: Endoglin
EPHB4: Ephrin Type-B Receptor 4
ESS: Epistaxis Severity Score
FGF: Fibroblast Growth Factor
FK506: Tacrolimus
GI: Gastrointestinal Bleeding
HHT: Hereditary Haemorrhagic Telangiectasia
iKO: inducible Knock Out
JPHT: Juvenile Polyposis/HHT
MADH4/Smad: Mothers AgainstDecapentaplegic Homolog 4
mRNA: messenger Ribonucleic Acid
NAC: N-acetylcysteine
OLT: Orthotopic Liver Transplant
OPG: Osteoprotegerin
PDGF: Platelet Derived Growth Factor
RANK: Receptor Activator of Nuclear Factor κ B

RANK-L: Receptor Activator of Nuclear Factor κ B Ligand

RASA1: RAS P21 ProteinActivator 1

SERMs: SelectiveEstrogen Receptor Modulator

TA: TranexamicAcid

TGF-β: Transforming Growth Factor β

VEGF: Vascular Endothelial Growth Factor

VM: Venous Malformation

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