haematologica
Journal of the Ferrata Storti Foundation

Integration of genotypic data into clinical trial design and reporting in hereditary hemorrhagic telangiectasia could help personalize treatment

by Atieh Modarresi and Claire L. Shovlin

Received: May 4, 2024.
Accepted: June 20, 2024.

Citation: Atieh Modarresi and Claire L. Shovlin. Integration of genotypic data into clinical trial design and reporting in hereditary hemorrhagic telangiectasia could help personalize treatment. Haematologica. 2024 June 27. doi: 10.3324/haematol.2024.285809 [Epub ahead of print]

Integration of genotypic data into clinical trial design and reporting in hereditary hemorrhagic telangiectasia could help personalize treatment

Atieh Modarresi[1] and Claire L. Shovlin[1,2,3]

[1] National Heart and Lung Institute, Imperial College London; London, UK; [2] NIHR Imperial Biomedical Research Centre; London, UK; [3]Imperial College Healthcare NHS Trust; London, UK.

Running Head: HHT genotypes and clinical trials

Corresponding Author: Claire L. Shovlin PhD FRCP, National Heart and Lung Institute, Imperial Centre for Translational and Experimental Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK. Email c.shovlin@imperial.ac.uk

Abbreviations:
Activin receptor-like kinase 1 (ACVRL1), endoglin (ENG), hereditary haemorrhagic telangiectasia (HHT), premature termination codons (PTCs), randomized-controlled trial (RCT)

Acknowledgements:
This work was supported by the NIHR Imperial Biomedical Research Centre, and the Alexandra Murphy HHT Foundation. The views expressed are those of the authors and not necessarily those of funders, the NHS, the NIHR, or the Department of Health and Social Care.

Hereditary hemorrhagic telangiectasia (HHT) is an inherited vascular malformation syndrome that has diverse consequences including recurrent bleeding which often results in anemia requiring iron supplementation or transfusion. Hemorrhage interventions range from nasal topical humidification, to oral agents such as tranexamic acid, local ablative treatments, and for patients still requiring intravenous iron supplementation or red cell transfusions, systemic anti-angiogenic therapies which have demonstrated promise in observational studies.[1,2] Randomized-controlled trials (RCTs) indicate benefit from topical saline, oral tranexamic acid, tamoxifen, and high dose oestrogen-progesterone.[1] The number of eligible patients limits the trial size for anti-angiogenic agents. This was evident in the only bevacizumab RCT, which, with 24 transfusion-dependent recruits, was underpowered due to interpatient heterogeneity and did not meet its primary endpoint.[3] This prompted us to explore across all reported HHT treatments, whether causal DNA mutations may affect patient responses to drug treatments utilized in HHT clinical trials.

HHT results from the disruption of the BMP9/BMP10 signalling pathway, due to loss-of-function mutations usually in endoglin (*ENG*) or activin receptor-like kinase 1 (*ACVRL1*).[4] Both genes encode proteins that are constituents of the BMP9 receptor complex, although pathogenic mutations are associated with subtly different clinical phenotypes, such as variations in the distribution of arteriovenous malformations.[2,5] Furthermore, there is variability in the type of loss-of-function mutations in these genes: in *ENG*, frameshift and nonsense mutations are predominant, leading to premature termination codons (PTCs), while *ACVRL1* shows a higher prevalence of missense substitutions.[6] Notably, a recent study of over 400 patients demonstrated that those with PTC-generating mutations exhibited different HHT bleeding patterns, supported by distinct endothelial cell phenotypes.[6]

Given the potential value of differentiating between causal DNA mutations in HHT treatment responses, our aim was to extract evidence from clinical trials that assess drug interventions for HHT. A comprehensive review of published clinical trials accessible through PubMed was performed using “Hereditary Haemorrhagic/Hemorrhagic Telangiectasia" as the MeSH Major Topic. We filtered search results for clinical trials and included trials investigating drug interventions. To gain further insight into the evolving landscape, ongoing clinical trials listed on https://clinicaltrials.gov/ were also reviewed.

We identified 50 HHT trials listed on PubMed, 27 of which involved drug interventions. Eleven studies utilized local routes of administration, with medications administered systemically in sixteen studies (Supplementary Table 1). HHT-causal genotypes were reported in 12/27 (44%) of trials, predominantly in those focusing on systemic drug intervention, with no discernible trend by publication date.

Only two trials considered HHT genotypic information when analysing treatment response.[7, 8] One was a pilot study evaluating the effect of N-acetylcysteine on 43 patients, where several response metrics differed between patients with *ENG* and *ACVRL1* mutations.[7] For example, the duration of daytime epistaxis reduced by 27.9% in the 23 *ENG* cases (p=0.02) compared to 6.7% in the 18 *ACVRL1* cases (p=0.7).[7] The second, smaller study assessed the anti-angiogenic drug thalidomide in 28 patients and reported significant reductions in multiple parameters of severe recurrent epistaxis. Comparing the 24 with *ACVRL1* and 4 with *ENG* mutations, there was no hint of a trend to different responses.[8]

Since only two published articles addressed HHT genotype-stratified responses, we explored whether more information is likely to emerge from clinical trials in progress. Out of 89

registered HHT clinical trials, we identified 41 trials that specifically focus on drug interventions. Of these, 24 have been completed (including 16 of the 27 studies already published in PubMed), 8 are currently ongoing, and 9 have been either withdrawn, terminated, or have an unknown status (Supplementary Table 2). Based on the information available on ClinicalTrials.gov, 28 May 2024, among the 8 ongoing trials, only one study (NCT03850964) stated a planned secondary outcome measure to examine the role of HHT genotype on the response to treatment. According to the available information, the remaining trials in progress primarily involve evaluating HHT cases as a single group, without specific mention of causal mutations.

These data show that despite widespread use of sequencing technologies in clinical diagnostics for HHT, stratifying outcomes based on the genetic subtype is not yet common practice at the design stage of HHT clinical trials. Where mutational data has been included in publications, this information was typically reported solely as baseline patient characteristics, as opposed to being considered as part of the analysis. This limitation may primarily be attributed to the small sample sizes and insufficient power of most HHT trials, making it difficult to detect differences in subgroup analysis. Other contributing factors include unknown mutational status in patients otherwise meeting study recruitment criteria, and lack of appreciation that there may be genotype-specific effects.

We identified two retrospective studies that used genotypic sub-analysis within larger sample sized studies in HHT.[9,10] The first study on bevacizumab found no difference in bleeding and anaemia based on pathogenic mutations.[9] The second study, focusing on the safety of bevacizumab and thalidomide, suggested that patients with *ENG* mutations might experience more adverse effects with thalidomide compared to bevacizumab.[10] While chance effects

resulting from limited sample sizes are possible, the findings from available RCTs and retrospective studies suggest that there may be an impact of HHT pathogenic mutations on some drug responses and adverse effects. The limited available data suggest that this impact may vary depending on the mechanism of action and the pathway targeted by the medication.

In general, conducting RCTs in rare diseases poses challenges due to small sample sizes and significant patient heterogeneity. While analysing by genotypic subgroups reduces case numbers and may be expected to reduce statistical power, where a confounder is removed leading to a smaller standard deviation, this increases the likelihood of detecting a difference if one exists. Therefore, in addition to strategies already utilised in HHT clinical trials, such as utilizing multi-centre or multinational centres, crossover or N-of-1 designs, we suggest attention is paid to HHT genotypes. Focusing on participants with specific loss-of-function mutations[6] may further mitigate heterogeneity.

In conclusion, we suggest that integrating genotypic data into clinical trial design and reporting, holds promise for enhancing detection of treatment benefits and development of more effective therapies for HHT-associated chronic bleeding.

References

1. 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.
2. Shovlin CL, Buscarini E, Sabbà C, et al. The European Rare Disease Network for HHT Frameworks for management of hereditary haemorrhagic telangiectasia in general and speciality care. Eur J Med Genet. 2022;65(1):104370.
3. Dupuis□Girod S, Rivière S, Lavigne C, et al. Efficacy and safety of intravenous bevacizumab on severe bleeding associated with hemorrhagic hereditary telangiectasia: A national, randomized multicenter trial. J Intern Med. 2023;294(6):761-774.
4. Al Tabosh T, Liu H, Koça D, et al. Impact of heterozygous ALK1 mutations on the transcriptomic response to BMP9 and BMP10 in endothelial cells from hereditary hemorrhagic telangiectasia and pulmonary arterial hypertension donors. Angiogenesis. 2024;27(2):211-227.
5. Al Tabosh T, Al Tarrass M, Tourvieilhe L, Guilhem A, Dupuis-Girod S, Bailly S. Hereditary hemorrhagic telangiectasia: from signaling insights to therapeutic advances. J Clin Invest. 2024;134(4):e176379.
6. Bernabéu-Herrero ME, Patel D, Bielowka A, et al. Mutations causing premature termination codons discriminate and generate cellular and clinical variability in HHT. Blood. 2024;143(22):2314-2331.
7. de Gussem EM, Snijder RJ, Disch FJ, Zanen P, Westermann CJ, Mager JJ. The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study. Rhinology. 2009;47(1):85-88.
8. Invernizzi R, Quaglia F, Klersy C, et al. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol. 2015;2(11):e465-473.
9. 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. 2021;106(8):2161-2169.
10. 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.

Integration of genotypic data into clinical trial design and reporting in hereditary hemorrhagic telangiectasia could help personalize treatment

Atieh Modarresi and Claire L. Shovlin

DATA SUPPLEMENT

Online Supplementary Table 1. Published clinical trials with drug interventions in PubMed

Administration	Intervention	Title	First author, year
Local	Bevacizumab[1]	Randomized, controlled, double-blinded clinical trial of effect of bevacizumab injection in management of epistaxis in hereditary hemorrhagic telangiectasia patients undergoing surgical cauterization	Khanwalkar, 2022
	Bevacizumab[2]	Intranasal submucosal bevacizumab for epistaxis in hereditary hemorrhagic telangiectasia: a double-blind, randomized, placebo-controlled trial	Riss, 2015
	Bevacizumab[3]	Effect of Bevacizumab Nasal Spray on Epistaxis Duration in Hereditary Hemorrhagic Telangiectasia: A Randomized Clinical Trial	Dupuis-Girod, 2016
	Bevacizumab, estriol, tranexamic acid 10%, or placebo[4]	Effect of Topical Intranasal Therapy on Epistaxis Frequency in Patients with Hereditary Hemorrhagic Telangiectasia: A Randomized Clinical Trial	Whitehead, 2016
	Bevacizumab[5]	ELLIPSE Study: a Phase 1 study evaluating the tolerance of bevacizumab nasal spray in the treatment of epistaxis in hereditary hemorrhagic telangiectasia	Dupuis-Girod, 2014
	Floseal®[6]	Prospective pilot study of Floseal® for the treatment of anterior epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT)	Lee, 2019
	Estrogen[7]	Intranasal topical estrogen in the management of epistaxis in hereditary hemorrhagic telangiectasia	Minami, 2016
	Timolol[8]	Efficacy of timolol in a novel intranasal thermosensitive gel for hereditary hemorrhagic telangiectasia-associated epistaxis: a randomized clinical trial	Peterson, 2020
	Timolol[9]	Efficacy of timolol nasal spray as a treatment for epistaxis in hereditary hemorrhagic telangiectasia. A double-blind, randomized, placebo-controlled trial	Dupuis-Girod, 2019
	Estriol[10]	Plasma surgery and topical estriol: Effects on the nasal mucosa and long-term results in patients with Osler's disease	Sadick, 2003
	Estrogens[11]	Topical estrogens combined with argon plasma coagulation in the management of epistaxis in hereditary hemorrhagic telangiectasia	Bergler, 2002
Systemic	Bevacizumab[12]	Efficacy and safety of intravenous bevacizumab on severe bleeding associated with hemorrhagic hereditary telangiectasia: A national, randomized multi-centre trial	Dupuis-Girod, 2023
	Bevacizumab[13]	Emerging role of bevacizumab in management of patients with symptomatic hepatic involvement in hereditary hemorrhagic telangiectasia	Chavan, 2017
	Bevacizumab[14]	Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output	Dupuis-Girod, 2012
	Carbazochrome-Sodium-Sulfonate[15]	An Old Drug for a New Application: Carbazochrome-Sodium-Sulfonate in HHT	Passali, 2015
	Doxycycline[16]	Randomized, double-blind, placebo-controlled, crossover trial of oral doxycycline for epistaxis in hereditary hemorrhagic telangiectasia	Thompson, 2022
	Doxycycline[17]	North American Study for the Treatment of Recurrent Epistaxis with Doxycycline: The NOSTRIL trial	McWilliams, 2022
	Estradiol valerate[18]	Estrogen treatment of hereditary hemorrhagic telangiectasia. A double-blind controlled clinical trial	Vase, 1981
	Ethinyl oestradiol and norethisterone[19]	Georges Brohee Prize. Oestrogen-progesterone, a new therapy of bleeding gastrointestinal vascular malformations	Van Cutsem, 1990
	Itraconazole[20]	Oral itraconazole for epistaxis in hereditary hemorrhagic telangiectasia: a proof of concept study	Kroon, 2021
	N-acetylcysteine[21]	The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study	de Gussem, 2009
	Octreotide[22]	Octreotide for gastrointestinal bleeding in hereditary hemorrhagic telangiectasia: A prospective case series	Kroon, 2019
	Pazopanib[23]	Pazopanib may reduce bleeding in hereditary hemorrhagic telangiectasia	Faughnan, 2019
	Tamoxifen[24]	Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo controlled clinical trial	Yaniv, 2009
	Thalidomide[25]	Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study	Invernizzi, 2015
	Tranexamic acid[26]	Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease	Gaillard, 2014
	Tranexamic acid[27]	Treatment of epistaxis in hereditary hemorrhagic telangiectasia with tranexamic acid - a double-blind placebo-controlled cross-over phase IIIB study	Geisthoff, 2014

Online Supplementary Table 2. Registered clinical trials with drug interventions on clinicaltrials.gov[28]

Administration	Intervention	Trial ID	Study title	Study status
Local	Bevacizumab	NCT01397695	Topical Bevacizumab for the Management of Recurrent Epistaxis in Patients With Hereditary Hemorrhagic Telangiectasia (HHT)	Completed
	Bevacizumab	NCT02106520	Efficacy of a Bevacizumab Nasal Spray as a Treatment for Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT)	Terminated
	Bevacizumab	NCT01507480	The ELLIPSE Study: A Phase-1 Study Evaluating the Tolerance of Bevacizumab Nasal Spray to Treat Epistaxis in Hereditary Hemorrhagic Telangiectasia	Completed
	Bevacizumab	NCT01314274	Intranasal Submucosal Bevacizumab for Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT)	Completed
	Bevacizumab	NCT02389959	Intranasal Bevacizumab for HHT-Related Epistaxis	Completed
	Bevacizumab	NCT01402531	Submucosal Bevacizumab for the Management of Recurrent Epistaxis in Patients With Hereditary Hemorrhagic Telangiectasia (HHT)	Completed
	Bevacizumab	NCT02157987	Treatment of Hereditary Hemorrhagic Telangiectasia of the Nasal Mucosa by Intranasal Bevacizumab: Search for Effective Dose	Unknown status
	Bevacizumab, Tranexamic Acid, Estriol, Sterile saline	NCT01408030	North American Study of Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT)	Completed
	Floseal®	NCT02638012	Prospective Pilot Study of Floseal for the Treatment of Anterior Epistaxis in Patients With (HHT)	Completed
	Mupirocin	NCT02963129	Treatment of Nasal Staphylococcus Aureus Colonization in Patients With HHT	Unknown status
	Propranolol	NCT04113187	Propranolol for Epistaxis in Hereditary Hemorrhagic Telangiectasia Patients	Completed
	Tacrolimus	NCT03152019	Efficacy and Safety of a 0.1% Tacrolimus Nasal Ointment as a Treatment for Epistaxis in Hemorrhagic Hereditary Telangiectasia (HHT)	Completed
	Timolol	NCT04139018	Timolol Gel for Epistaxis in Hereditary Hemorrhagic Telangiectasia	Completed
	Timolol	NCT02484716	Efficacy of a Timolol Nasal Spray as a Treatment for Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT) - (TEMPO)	Completed
	Timolol	NCT01752049	Topical Anti-angiogenic Therapy for Telangiectasia in HHT: Proof of Concept	Completed
Systemic	Bevacizumab	NCT04404881	Bevacizumab In Hereditary Hemorrhagic Telangiectasia	Recruiting
	Bevacizumab	NCT03227263	BABH Study: Efficacy and Safety of Bevacizumab on Severe Bleedings Associated With Hemorrhagic Hereditary Telangiectasia (HHT).	Completed
	Bevacizumab	NCT00843440	Efficacy and Safety of Bevacizumab for the Treatment Hemorrhagic Hereditary Telangiectasia (HHT) Associated With Severe Hepatic Vascular Malformations. Phase II Study	Completed
	Doxycycline	NCT04167085	NOrth American Study for the Treatment of Recurrent epIstaxis With DoxycycLine: The NOSTRIL Trial	Completed
	Doxycycline	NCT03397004	Doxycycline for Hereditary Hemorrhagic Telangiectasia	Active, not recruiting
	Ferrous sulphate	NCT01908543	Iron Deficiency and Hereditary Haemorrhagic Telangiectasia	Terminated
	Nintedanib	NCT04976036	Efficacy of Nintedanib for Treatment of Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT) Patients	Recruiting
	Nintedanib	NCT03954782	Efficacy of Nintedanib Per os as a Treatment for Epistaxis in HHT Disease.	Completed
	Octreotide	NCT00004327	Phase II Pilot Study of Octreotide, a Somatostatin Octapeptide Analog, for Gastrointestinal Hemorrhage in Hormone-Refractory Hereditary Hemorrhagic Telangiectasia and Senile Ectasia	Completed
	Octreotide LAR	NCT02874326	Octreotide in Patients With GI Bleeding Due to Rendu-Osler-Weber	Unknown status
	Pazopanib	NCT03850730	Pazopanib for the Treatment of Epistaxis in Hereditary Hemorrhagic Telangiectasia	Not yet recruiting
	Pazopanib	NCT03850964	Effects of Pazopanib on Hereditary Hemorrhagic Telangiectasia Related Epistaxis and Anemia (Paz)	Recruiting
	Pazopanib	NCT02204371	Evaluation of Pazopanib on Bleeding in Subjects With Hereditary Haemorrhagic Telangiectasia	Terminated
	Pegylated Interferon Alpha2b	NCT00588146	Phase 2 Study of PEG-Intron in Hereditary Hemorrhagic Telangiectasia	Terminated
	Pomalidomide	NCT02287558	Pomalidomide in Hereditary Hemorrhagic Telangiectasia and Transfusion-Dependent Vascular Ectasia: a Phase I Study	Completed
	Pomalidomide	NCT03910244	Pomalidomide for the Treatment of Bleeding in HHT	Completed

	Ranibizumab	NCT01406639	Ranibizumab for the Management of Recurrent Nosebleeds in Patients With Hereditary Hemorrhagic Telangiectasia (HHT)	Withdrawn
	Sirolimus	NCT05269849	Sirolimus for Nosebleeds in HHT	Recruiting
	Tacrolimus	NCT04646356	Tacrolimus Trial for Hereditary Hemorrhagic Telangiectasia (HHT)	Active, not recruiting
	Tamoxifen	NCT00375622	Anti-Estrogen Therapy for Hereditary Hemorrhagic Telangiectasia A Double-Blind Placebo-Controlled Clinical Trial	Completed
	Thalidomide	NCT01485224	Efficacy of Thalidomide in the Treatment of Hereditary Hemorrhagic Telangiectasia	Completed
	Thalidomide	NCT00389935	Thalidomide Reduces Arteriovenous Malformation Related Gastrointestinal Bleeding	Completed
	Tranexamic acid	NCT00355108	ATERO: A Randomised Study With Tranexamic Acid in Epistaxis of Rendu Osler Syndrome	Completed
	Tranexamic acid	NCT01031992	Tranexamic Acid and Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT)	Completed
	VAD044	NCT05406362	Assess Safety and Efficacy of VAD044 in HHT Patients	Recruiting
	Vit D	NCT03981562	Vitamin D and Hereditary Haemorrhagic Telangiectasia	Unknown status

Supplementary References

1. Khanwalkar AR, Rathor A, Read AK, Paknezhad H, Ma Y, Hwang PH. Randomized, controlled, double-blinded clinical trial of effect of bevacizumab injection in management of epistaxis in hereditary hemorrhagic telangiectasia patients undergoing surgical cauterization. Int Forum Allergy Rhinol. 2022;12(8):1034-1042.
2. Riss D, Burian M, Wolf A, Kranebitter V, Kaider A, Arnoldner C. Intranasal submucosal bevacizumab for epistaxis in hereditary hemorrhagic telangiectasia: a double-blind, randomized, placebo-controlled trial. Head Neck. 2015;37(6):783-787.
3. Dupuis-Girod S, Ambrun A, Decullier E, et al. Effect of Bevacizumab Nasal Spray on Epistaxis Duration in Hereditary Hemorrhagic Telangectasia: A Randomized Clinical Trial. JAMA. 2016;316(9):934-942.
4. Whitehead KJ, Sautter NB, McWilliams JP, et al. Effect of Topical Intranasal Therapy on Epistaxis Frequency in Patients With Hereditary Hemorrhagic Telangiectasia: A Randomized Clinical Trial. JAMA. 2016;316(9):943-951.
5. Dupuis-Girod S, Ambrun A, Decullier E, et al. ELLIPSE Study: a Phase 1 study evaluating the tolerance of bevacizumab nasal spray in the treatment of epistaxis in hereditary hemorrhagic telangiectasia. MAbs. 2014;6(3):794-799.
6. Lee JM, Wu V, Faughnan ME, Lasso A, Figol A, Kilty SJ. Prospective pilot study of Floseal® for the treatment of anterior epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT). J Otolaryngol Head Neck Surg. 2019;48(1):48.
7. Minami K, Haji T. Intranasal topical estrogen in the management of epistaxis in hereditary hemorrhagic telangiectasia. Acta Otolaryngol. 2016;136(5):528-531.
8. Peterson AM, Lee JJ, Kallogjeri D, Schneider JS, Chakinala MM, Piccirillo JF. Efficacy of Timolol in a Novel Intranasal Thermosensitive Gel for Hereditary Hemorrhagic Telangiectasia-Associated Epistaxis: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2020;146(11):1006-1014.
9. Dupuis-Girod S, Pitiot V, Bergerot C, et al. Efficacy of TIMOLOL nasal spray as a treatment for epistaxis in hereditary hemorrhagic telangiectasia. A double-blind, randomized, placebo-controlled trial. Sci Rep. 2019;9(1):11986.
10. Sadick H, Naim R, Oulmi J, Hörmann K, Bergler W. Plasma surgery and topical estriol: effects on the nasal mucosa and long-term results in patients with Osler's disease. Otolaryngol Head Neck Surg. 2003;129(3):233-238.
11. Bergler W, Sadick H, Gotte K, Riedel F, Hörmann K. Topical estrogens combined with argon plasma coagulation in the management of epistaxis in hereditary hemorrhagic telangiectasia. Ann Otol Rhinol Laryngol. 2002;111(3 Pt 1):222-228.
12. Dupuis-Girod S, Rivière S, Lavigne C, et al. Efficacy and safety of intravenous bevacizumab on severe bleeding associated with hemorrhagic hereditary telangiectasia: A national, randomized multicenter trial. J Intern Med. 2023;294(6):761-774.
13. Chavan A, Schumann-Binarsch S, Schmuck B, et al. Emerging role of bevacizumab in management of patients with symptomatic hepatic involvement in Hereditary Hemorrhagic Telangiectasia. Am J Hematol. 2017;92(11):E641-e644.
14. 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.
15. Passali GC, De Corso E, Bastanza G, Di Gennaro L. An old drug for a new application: carbazochrome-sodium-sulfonate in HHT. J Clin Pharmacol. 2015;55(5):601-602.
16. Thompson KP, Sykes J, Chandakkar P, et al. Randomized, double-blind, placebo-controlled, crossover trial of oral doxycycline for epistaxis in hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis. 2022;17(1):405.
17. McWilliams JP, Majumdar S, Kim GH, et al. North American Study for the Treatment of Recurrent Epistaxis with Doxycycline: The NOSTRIL trial. J Thromb Haemost. 2022;20(5):1115-1125.
18. Vase P. Estrogen Treatment of Hereditary Hemorrhagic Telangiectasia. Acta Med Scand. 1981;209(1-6):393-396.
19. van Cutsem E, Rutgeerts P, Vantrappen G. Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. Lancet. 1990 Apr 21;335(8695):953-5.
20. Kroon S, Snijder RJ, Hosman AE, et al. Oral itraconazole for epistaxis in hereditary hemorrhagic telangiectasia: a proof of concept study. Angiogenesis. 2021;24(2):379-386.
21. de Gussem EM, Snijder RJ, Disch FJ, Zanen P, Westermann CJ, Mager JJ. The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study. Rhinology. 2009;47(1):85-88.
22. Kroon S, Snijder RJ, Mager JJ, et al. Octreotide for gastrointestinal bleeding in hereditary hemorrhagic telangiectasia: A prospective case series. Am J Hematol. 2019;94(9):E247-e249.

23. Faughnan ME, Gossage JR, Chakinala MM, et al. Pazopanib may reduce bleeding in hereditary hemorrhagic telangiectasia. Angiogenesis. 2019;22(1):145-155.
24. Yaniv E, Preis M, Hadar T, Shvero J, Haddad M. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. Laryngoscope. 2009;119(2):284-288.
25. Invernizzi R, Quaglia F, Klersy C, et al. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol. 2015;2(11):e465-473.
26. Gaillard S, Dupuis-Girod S, Boutitie F, et al. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. J Thromb Haemost. 2014;12(9):1494-1502.
27. Geisthoff UW, Seyfert UT, Kübler M, Bieg B, Plinkert PK, König J. Treatment of epistaxis in hereditary hemorrhagic telangiectasia with tranexamic acid - a double-blind placebo-controlled cross-over phase IIIB study. Thromb Res. 2014;134(3):565-571.
28. National Library of Medicine, National Center for Biotechnology Information. ClinicalTrials.gov available at https://clinicaltrials.gov/, accessed 28 May 2024.