Türkiye Klinikleri Tıp Bilimleri Dergisi
Turkiye Klinikleri Journal of Medical Sciences
Turkiye Klinikleri J Med Sci. 2023;43(3):281-6

ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/medsci.2023-96203

Course of Treatment of Chronic Bleeding and Anemia with Systemic Bevacizumab Treatment in Hereditary Hemorrhagic Telangiectasia: A Retrospective Cohort

Herediter Hemorajik Telenjiyektazide Sistemik Bevasizumab Tedavisiyle Kronik Kanama ve Anemi Tedavisinin Seyri: Bir Retrospektif Kohort

Emine DURAK[a], Mehmet Can UĞUR[b], Füsun GEDİZ[c]

[a]Department of Hematology, Abant İzzet Baysal University İzzet Baysal Training and Research Hospital, Bolu, Türkiye
[b]Department of Hematology, İzmir Bakırçay University Çiğli Training and Research Hospital, İzmir, Türkiye
[c]Department of Internal Medicine, İzmir University of Economics Medicalpoint Hospital, İzmir, Türkiye

ABSTRACT Objective: Hereditary hemorrhagic telangiectasia (HHT), is an autosomal dominant disorder that causes abnormal angiogenesis. Interest in targeted therapies has been increasing in recent years, especially for the treatment of severe forms of HHT. One of these treatment options is the vascular endothelial growth factor inhibitor bevacizumab. Purpose of this study is to investigate the effect of systemic bevacizumab use on the treatment of chronic bleeding course and anemia in patients diagnosed with HHT. **Material and Methods:** The treatment response and adverse events of patients with bevacizumab were evaluated retrospectively. **Results:** The mean age was 51,5. Mean duration of treatment was 15.4 (4-25 months) months. The first 4 doses of 5 mg/kg intravenous bevacizumab were administered at 2-week intervals in all patients. Bevacizumab maintenance continued at a dose of 5 mg/kg in monthly periods. With bevacizumab treatment, an increase in hemoglobin values, a decrease in epistaxis severity score, parenteral iron and erythrocyte transfusion requirement were achieved. Side effects observed were allergic rash in one patient and arthralgia in one patient. None of the patients required discontinuation of treatment due to side effects. **Conclusion:** Bevacizumab is a promising treatment option in HHT, which can be mortal if not controlled. However, there remains a need for more comprehensive studies in order to achieve a global consensus on treatment protocols and management of adverse events.

Keywords: Bevacizumab; hereditary hemorrhagic telangiectasia; epistaxis

ÖZET Amaç: Kalıtsal hemorajik telenjiyektazi (HHT), anormal anjiyogeneze neden olan otozomal dominant bir hastalıktır. Son yıllarda, özellikle şiddetli HHT formlarının tedavisi için hedefe yönelik tedavilere olan ilgi artmaktadır. Bu tedavi seçeneklerinden biri de vasküler endotelyal büyüme faktörü inhibitörü bevasizumabtır. Bu çalışmanın amacı, HHT tanısı alan hastalarda sistemik bevasizumab kullanımının kronik kanama seyri ve anemi tedavisindeki etkisini araştırmaktır. **Gereç ve Yöntemler:** Bevasizumab kullanan hastaların tedavi yanıtı ve yan etkileri retrospektif olarak değerlendirildi. **Bulgular:** Hastaların yaş ortalaması 51,5 yıl idi. Ortalama tedavi süresi 15,4 (4-25 ay) aydı. Tüm hastalara 2 hafta arayla ilk 4 doz 5 mg/kg intravenöz bevasizumab uygulandı. Bevasizumab idamesi 5 mg/kg dozunda aylık periyotlarla devam etti. Bevasizumab tedavisi ile hemoglobin değerlerinde artış, epistaksis şiddet skorunda parenteral demir ve eritrosit transfüzyon gereksiniminde azalma sağlandı. Gözlenen yan etkiler, 1 hastada alerjik döküntü ve 1 hastada artralji idi. Yan etkiler nedeniyle hiçbir hastada tedavinin kesilmesi gerekmedi. **Sonuç:** Bevasizumab, kontrol edilmediği takdirde ölümcül olabilen HHT'de umut verici bir tedavi seçeneğidir. Bununla birlikte, tedavi protokolleri ve advers olayların yönetimi konusunda global konsensus sağlamak için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Bevasizumab; herediter hemorajik telenjiyektazi; epistaksis

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a common autosomal dominant disorder that causes abnormal angiogenesis. Its prevalence has been reported as 1/5,000 in North America. However, since the diagnosis is often missed and some patients may be asymptomatic, the actual prevalence of the disease is estimated to be higher.[1,2] In the pathogenesis of the

Correspondence: Mehmet Can UĞUR
Department of Hematology, İzmir Bakırçay University Çiğli Training and Research Hospital, İzmir, Türkiye
E-mail: med.can@hotmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Medical Sciences.

Received: 20 Feb 2023 ***Received in revised form:*** 13 May 2023 ***Accepted:*** 18 May 2023 ***Available online:*** 02 Jun 2023

disease, vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β) levels increase and cause abnormal angiogenesis as a result of mutations in *ENG*, *ALK1* and *SMAD4* genes and hence, activation of Smad4 signaling pathway (VEGF) through anaplastic lymphoma kinase (ALK)-1 and ALK-5 receptors.[3] While the most frequently detected genetic mutation is in the *ENG* gene (61%), *ALK1* and *SMAD4* gene mutations are found in 37% and 2%, respectively. However, while a mutation can be identified in 80% of the cases, the diagnosis is made based on clinical findings in 20%.[4,5]

Clinical symptoms are arteriovenous malformations (AVM), mucocutaneous telangiectasias, and iron deficiency anemia as a result of chronic blood loss. Pulmonary AVM can cause hemoptysis, dyspnea and heart failure with high out-put, hepatic AVM can cause chronic liver failure and portal hypertension, while AVM in the central nervous system can cause symptoms such as epilepsy, transient ischemic attack and stroke.[6-8] Epistaxis and gastrointestinal bleeding are the most common causes of chronic blood loss and iron deficiency.[9]

Curaçao criteria, which include spontaneous and recurrent epistaxis, characteristic localized telangiectasias, visceral arteriovenous malformations, and a history of HHT in a first-degree relative are used for diagnosis. Patients with 3 or 4 of these criteria are diagnosed with HHT.[10]

Interest in targeted therapies has been increasing in recent years, especially for the treatment of severe forms of HHT. Increasing scientific evidence for bevacizumab, a humanized antibody against VEGF used in the treatment of various types of cancer, indicates the efficacy and safety of this treatment option.[11,12]

PURPOSE

Purpose of this study is to investigate the effect of systemic bevacizumab use on the treatment of chronic bleeding course and anemia in patients diagnosed with HHT.

MATERIAL AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from University of Health Sciences Bozyaka Training and Research Hospital Ethics Committee (date: July 28, 2021, no: 2021/130). Patients over the age of 18 who were diagnosed with HHT according to Curaçao criteria and administered with bevacizumab treatment in the hematology clinic of the same center were included in the study.[10] Patients' age, sex, comorbidities, genetic mutation, AVM foci and primary bleeding focus, bevacizumab dose, duration and treatment-related side effects, epistaxis severity score (ESS) at diagnosis, 3rd, 6th, and 12th months, hemoglobin level, requirements for parenteral iron and erythrocyte transfusion information were recorded by retrospectively reviewing the patient files.

ESS is a scoring system calculated by using the parameters of epistaxis frequency, bleeding duration, intensity, need for medical support, development of anemia, and need for erythrocyte transfusion of the patients diagnosed with HHT.[13] As the ESS score increases, the frequency and severity of epistaxis also increase. In our study, ESS scores were calculated with the help of the calculator on the www.curehht.org website.

STATISTICS

Due to the small sample size, the data was analyzed only by descriptive statistical methods.

RESULTS

Seven patients were included in the study. The mean age was 51.5. Small mothers against decapentaplegic 4 (SMAD4) mutation was detected in 3 patients. Telangiectasias and arteriovenous malformations were found in the gastrointestinal tract in one of the cases with SMAD4 mutation, but polyposis coli was not found. Information on age, sex, comorbidities, genetic mutation, AVM and telangiectasia foci, and primary bleeding focus of the patients are shown in Table 1.

The first 4 doses of 5 mg/kg intravenous bevacizumab were administered at 2-week intervals in all patients. Bevacizumab maintenance continued at a dose of 5 mg/kg in monthly periods. Iron carboxymaltose 500 mg vial was used for parenteral iron re-

TABLE 1: Age, sex, comorbidities, genetic mutation, AVM and telangiectasia foci, primary bleeding focus.

Patient no	Age	Sex	Mutation	Bleeding focus	AVM* and telangiectasia	Comorbidity
1	62	M*	Not studied	Epistaxis, GIS*	AVM in the colon, telangiectasia in the jejunum	CHF*, AF*, COPD*
2	45	M	SMAD4	Epistaxis, GIS	AVM in the rectum	Hypertension
3	50	F*	SMAD4	Epistaxis	AVM in the nasal septum	None
4	55	F	SMAD4	Epistaxis	None	None
5	43	M	Not studied	GIS	Telangiectasia in corpus and antrum	Ankylosing spondylitis
6	40	M	Not studied	Epistaxis	Telangiectasia in nasal septum	None
7	60	F	Not studied	Epistaxis	Telangiectasia in nasal septum	CHF and AF

* AVM: Arteriovenous malformation; AF: Atrial fibrillation; GIS: Gastrointestinal system; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; F: Female; M: Male.

placement that was administered when needed during follow-ups. Mean duration of treatment was 15.4 (4-25 months) months. The mean hemoglobin level which was 7,7 g/dL at the time of diagnosis increased to 12,1 g/dL while the mean ESS score decreased from 5,6 to 2,4. The mean monthly erythrocyte transfusion in the last 1 year was 2.3 and it decreased to 0.5 with bevacizumab treatment. Also, the mean monthly parenteral iron requirement in the last 1 year was 1,785 mg/month and decreased to 570 mg/month with treatment. The ESS score, hemoglobin level, parenteral iron and erythrocyte transfusion requirement of patients at diagnosis, 3rd, 6th and 12th months are shown in Figure 1.

The mean hemoglobin level of patients with SMAD4 mutation increased from 8.6 g/dL to 14.4 g/dL at the end of 12 months. While the mean ESS score decreased from 6.8 to 0.6, the patients no longer needed erythrocytes or parenteral iron.

Side effects observed were allergic rash in one patient and arthralgia in one patient. None of the patients required discontinuation of treatment due to side effects.

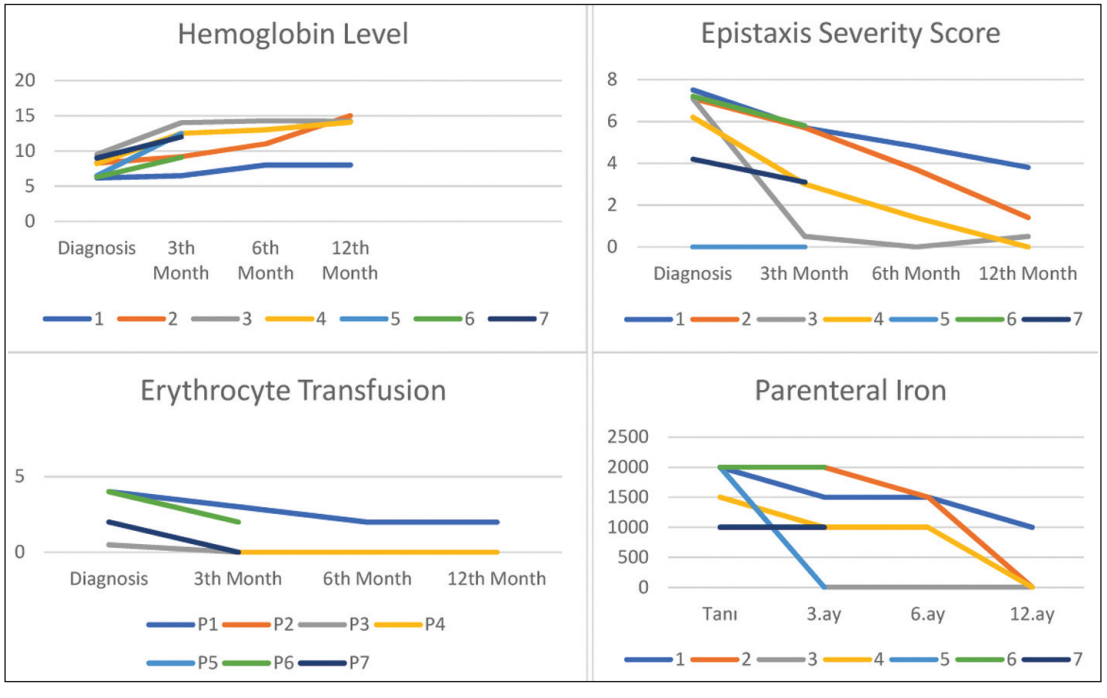

FIGURE 1: ESS score, hemoglobin level, parenteral iron and erythrocyte transfusion requirement at diagnosis, 3rd, 6th and 12th months. ESS: Epistaxis severity score.

DISCUSSION

HHT is an autosomal dominant hereditary disease that is caused by mutations in the endoglin (ENG) or activin receptor-like kinase 1 (ACVRL1/ALK1) and *SMAD4* genes belonging to the TGF-β superfamily, leading to a systemic angiogenic dysregulation. It causes changes in the TGF-β response of endothelial cells and leads to disruptions in angiogenesis. There are differences in the phenotypes of patients according to the underlying pathogenic gene. Frequently encountered *ENG* gene polymorphisms are associated with pulmonary arteriovenous malformations, and *ACVRL1* gene polymorphisms are associated with liver arteriovenous malformations.[14] The SMAD4 mutation, which was found in 3 patients in our study, is a rare mutation seen in approximately 2% of HHT cases. Polyposis coli and aortic dilatation may accompany HHT in these cases. However, it is not clear how affects the clinical course of HHT.[15] In Danish retrospective nationwide study, 76 per cent of these fulfilled the Curaçao criteria, 86% experienced recurrent epistaxis and 83% presented with telangiectatic lesions at different anatomical localisations. Almost 60% had AVMs, mainly pulmonary and hepatic, while none was found to have cerebral AVMs. Fifteen per cent had thoracic aortic abnormalities.[16]

As a result of these processes, hemorrhages due to angiogenic dysregulation and the resulting anemia constitute the basic clinic of the disease. End-stage renal disease, sepsis, and catastrophic bleeding that occur with the progression of the disease are the most common causes of mortality.[17]

Different treatment alternatives have been tried in the treatment of HHT. Tranexamic acid improved the severity of epistaxis compared to placebo, but failed to increase haemoglobin.[18] Treatments such as topical and oral estrogen and timolol have not been successful compared to placebo.[19-21]

In a murine study, it was found that VEGF blood level was higher in the HHT branch compared to the control group, and this situation was responsible for the persistence of angiogenesis.[22] Based on this information obtained, bevacizumab, a recombinant humanized monoclonal IgG1 antibody that neutralizes VEGF in circulation and is currently used in the treatment of diseases such as age-related macular degeneration, has started to be used off-label on a case-by-case basis, especially in the management of bleeding and anemia.[23,24] Since the nasal application of bevacizumab could not improve the severity of epistaxis, systemic application was frequently discussed on a case-by-case basis.[25]

A large number of retrospective or prospective studies have been published which investigate the use of systemic bevacizumab in the treatment of HHT-related bleeding and anemia.[11,17] In these studies, bevacizumab was found to be successful in terms of bleeding severity, erythrocyte and iron replacement requirement, and hemoglobin increase. InHIBIT, the largest study conducted, evaluated the results of 238 patients from 12 centers.[26] In this study, an increase in the mean hemoglobin level, a decrease in ESS, and a decrease in the need for erythrocyte and iron infusion were found with a median 12-month use of bevacizumab. These results obtained are independent of pathogenic mutation.

There is no clear consensus in the literature in terms of the treatment strategy. Induction therapy for 4-6 weeks followed by maintenance therapy is the main approach. Although doses and intervals vary for induction, 5-10 mg/kg per month is accepted as the general approach. Continuous and intermittent maintenance strategies are also discussed in terms of maintenance treatment. Although successful results are obtained with both methods, continuous treatment seems to be superior to intermittent treatment in terms of hemoglobin levels and ESS scores. However, there is no definite information regarding the cost-effectiveness of continuous treatment.[26]

When bevacizumab is evaluated in terms of safety profile, drug-related adverse events were reported in 38% of patients in the InHIBIT study. The most common adverse events were hypertension (18%), fatigue (10%), proteinuria (9%), myalgia and/or arthralgia (6%), headache (4%), and venous thromboembolism (2%). In the study of Guilhem et al., delay in wound healing was reported as an im-

portant side effect in addition to these side effects.[17] In our study, one patient had an allergic rash and one had arthralgia, however, these side effects could be managed with symptomatic treatments and did not require discontinuation of the treatment.

CONCLUSION

Bevacizumab is a promising treatment option in HHT, which can be mortal if not controlled. However, there remains a need for more comprehensive studies in order to achieve a global consensus on treatment protocols and management of adverse events.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Emine Durak;* ***Design:*** *Emine Durak, Füsun Gediz;* ***Control/Supervision:*** *Füsun Gediz;* ***Data Collection and/or Processing:*** *Emine Durak, Mehmet Can Uğur;* ***Analysis and/or Interpretation:*** *Mehmet Can Uğur;* ***Literature Review:*** *Mehmet Can Uğur;* ***Writing the Article:*** *Mehmet Can Uğur, Emine Durak;* ***Critical Review:*** *Füsun Gediz.*

REFERENCES

1. Marchuk DA. Genetic abnormalities in hereditary hemorrhagic telangiectasia. Curr Opin Hematol. 1998;5(5):332-8. [Crossref] [PubMed]
2. Westermann CJ, Rosina AF, De Vries V, de Coteau PA. The prevalence and manifestations of hereditary hemorrhagic telangiectasia in the Afro-Caribbean population of the Netherlands Antilles: a family screening. Am J Med Genet A. 2003;116A(4):324-8. [Crossref] [PubMed]
3. Kritharis A, Al-Samkari H, Kuter DJ. Hereditary hemorrhagic telangiectasia: diagnosis and management from the hematologist's perspective. Haematologica. 2018;103(9):1433-43. [Crossref] [PubMed] [PMC]
4. Richards-Yutz J, Grant K, Chao EC, Walther SE, Ganguly A. Update on molecular diagnosis of hereditary hemorrhagic telangiectasia. Hum Genet. 2010;128(1):61-77. [Crossref] [PubMed]
5. Kühnel T, Wirsching K, Wohlgemuth W, Chavan A, Evert K, Vielsmeier V. Hereditary Hemorrhagic Telangiectasia. Otolaryngol Clin North Am. 2018;51(1):237-54. [Crossref] [PubMed]
6. Brydon HL, Akinwunmi J, Selway R, Ul-Haq I. Brain abscesses associated with pulmonary arteriovenous malformations. Br J Neurosurg. 1999;13(3):265-9. [Crossref] [PubMed]
7. Cho D, Kim S, Kim M, Seo YH, Kim W, Kang SH, et al. Two cases of high output heart failure caused by hereditary hemorrhagic telangiectasia. Korean Circ J. 2012;42(12):861-5. [Crossref] [PubMed] [PMC]
8. Jessurun GA, Kamphuis DJ, van der Zande FH, Nossent JC. Cerebral arteriovenous malformations in The Netherlands Antilles. High prevalence of hereditary hemorrhagic telangiectasia-related single and multiple cerebral arteriovenous malformations. Clin Neurol Neurosurg. 1993;95(3):193-8. [Crossref] [PubMed]
9. AAssar OS, Friedman CM, White RI Jr. The natural history of epistaxis in hereditary hemorrhagic telangiectasia. Laryngoscope. 1991;101(9):977-80. [Crossref] [PubMed]
10. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000;91(1):66-7. [Crossref] [PubMed]
11. Iyer VN, Apala DR, Pannu BS, Kotecha A, Brinjikji W, Leise MD, et al. Intravenous bevacizumab for refractory hereditary hemorrhagic telangiectasia-related epistaxis and gastrointestinal bleeding. Mayo Clin Proc. 2018;93(2):155-66. Erratum in: Mayo Clin Proc. 2018;93(3):396. [Crossref] [PubMed]
12. Kjeldsen Jens, Fialla Annette D, Tine Rosenberg ADK. Bevacizumab as treatment of bleeding in patients with hereditary haemorrhagic telangiectasia (HHT). Gastroenterology. 2018;154:S701-2. [Crossref]
13. Yin LX, Reh DD, Hoag JB, Mitchell SE, Mathai SC, Robinson GM, et al. The minimal important difference of the epistaxis severity score in hereditary hemorrhagic telangiectasia. Laryngoscope. 2016;126(5):1029-32. [Crossref] [PubMed]
14. Lesca G, Olivieri C, Burnichon N, Pagella F, Carette MF, Gilbert-Dussardier B, et al; French-Italian-Rendu-Osler Network. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. Genet Med. 2007;9(1):14-22. [Crossref] [PubMed]
15. Shovlin CL, Simeoni I, Downes K, Frazer ZC, Megy K, Bernabeu-Herrero ME, et al. Mutational and phenotypic characterization of hereditary hemorrhagic telangiectasia. Blood. 2020;136(17):1907-18. [Crossref] [PubMed] [PMC]
16. Jelsig AM, Kjeldsen A, Christensen LL, Bertelsen B, Karstensen JG, Brusgaard K, et al. Hereditary haemorrhagic telangiectasia in Danish patients with pathogenic variants in SMAD4: a nationwide study. J Med Genet. 2023;60(5):464-8. [Crossref] [PubMed]
17. Guilhem A, Fargeton AE, Simon AC, Duffau P, Harle JR, Lavigne C, et al. Intra-venous bevacizumab in hereditary hemorrhagic telangiectasia (HHT): a retrospective study of 46 patients. PLoS One. 2017;12(11):e0188943. [Crossref] [PubMed] [PMC]
18. Gaillard S, Dupuis-Girod S, Boutitie F, Rivière S, Morinière S, Hatron PY, et al; ATERO Study Group. 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):1494-502. [Crossref] [PubMed]

19. Vase P. Estrogen treatment of hereditary hemorrhagic telangiectasia. A double-blind controlled clinical trial. Acta Med Scand. 1981;209(5):393-6. [Crossref] [PubMed]

20. Whitehead KJ, Sautter NB, McWilliams JP, Chakinala MM, Merlo CA, Johnson MH, et al. Effect of topical intranasal therapy on epistaxis frequency in patients with hereditary hemorrhagic telangiectasia: a randomized clinical trial. JAMA. 2016;316(9):943-51. [Crossref] [PubMed]

21. Dupuis-Girod S, Pitiot V, Bergerot C, Fargeton AE, Beaudoin M, Decullier E, 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. [Crossref] [PubMed] [PMC]

22. Cirulli A, Liso A, D'Ovidio F, Mestice A, Pasculli G, Gallitelli M, et al. Vascular endothelial growth factor serum levels are elevated in patients with hereditary hemorrhagic telangiectasia. Acta Haematol. 2003;110(1):29-32. [Crossref] [PubMed]

23. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology. 2005;112(6):1035-47. [Crossref] [PubMed]

24. Bose P, Holter JL, Selby GB. Bevacizumab in hereditary hemorrhagic telangiectasia. N Engl J Med. 2009;360(20):2143-4. [Crossref] [PubMed]

25. Dupuis-Girod S, Ambrun A, Decullier E, Fargeton AE, Roux A, Bréant V, et al. Effect of bevacizumab nasal spray on epistaxis duration in hereditary hemorrhagic telangectasia: a randomized clinical trial. JAMA. 2016;316(9):934-42. [Crossref] [PubMed]

26. Al-Samkari H, Kasthuri RS, Parambil JG, Albitar HA, Almodallal YA, Vázquez C, et al. An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study. Haematologica. 2021;106(8):2161-9. [Crossref] [PubMed] [PMC]