Treatments For Refractory HHT-Associated Epistaxis
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Tranexamic Acid (Lysteda)

Tranexamic acid is an antifibrinolytic, which reduces the breakdown of blood clots and helps to prevent prolonged bleeding. Tranexamic acid is used for HHT patients with persistent nosebleeds or anemia. Tranexamic acid should not be used in patients with history of bleeding in the brain (subarachnoid hemorrhage), history of blood clots (such as in the legs, lung, brain, eye), certain heart diseases (irregular heartbeat, heart valve problems), blood clotting problems, or kidney problems (including blood in the urine) after thorough discussion of risks and benefits. Oral formulation more effective than topical.

Side effects may include nausea, vomiting, diarrhea, vertigo, and muscle pain. Increased risk for blood clots.

Screen for elevated levels of Factor VIII and von Willebrand factor antigen prior to initiating oral TXA.

Standard dosing is 1.0-gram TID, 1.5 gm BID, 1.3 gm TID

Doxycycline

Doxycycline is an antibiotic, which has additional anti-inflammatory properties and reduction in angiogenesis or blood vessel growth. Limited research suggest it may have some benefit in the reduction of epistaxis in HHT patients.

Side effects may include: weight loss, nausea, vomiting, diarrhea, rash, skin sensitivity to sunlight, hives, anemia, and vaginal yeast infection

Standard dosing: 100 mg BID for 10-14 days (most people see a result in about a week) and then reduce dosing to 20mg BID.

Sclerotherapy

Sclerotherapy is the use of chemicals, like Sotradecol, to create irritation in the inner layers of the blood vessel wall. Injection of the sclerosing agent followed by pressure leads to obliteration of the lumen by inflammation and fibrosis. The process of inflammation resolves by fibrosis and takes around 6 months.

Sclerotherapy is widely considered the optimum treatment for reticular veins and telangiectasias. Office-based sclerotherapy is extremely effective for HHT-associated epistaxis. Patients tolerate the procedure well. Complications exceedingly rare, but can be serious. Meticulous technique and adherence to low-pressure injection with foam to reduce risk.

Timolol

Eye drops - Propranolol 0.5% nasal formulation

Topical gel

Timolol nasal gel 0.1% prepared with a poloxamer gel (combination of poloxamer 188 and 407; pH adjusted to 4.5-6.5) and 0.5 ml applied to each nostril twice daily. The total daily dose is about 2 mg. Prepared by Advanced Rx Pharmacy, Plymouth Meeting, Pennsylvania.

Contraindications for systemic β adrenergic blocker administration: Hypersensitivity to β adrenergic blockers, asthma or bronchospasm, congestive heart failure with LVEF <40%, hereditary pulmonary arterial hypertension, baseline bradycardia (HR <55 beats per minute), Sick Sinus Syndrome, 2nd or 3rd degree heart block, left or right bundle branch block, or bifasicular block, uncontrolled diabetes mellitus (most recent HbA1c >9%) or diabetic ketoacidosis within last 6 months, hypotension (systolic blood pressure < 90), known hypersensitivity to timolol, severe peripheral circulatory disturbances (Raynaud phenomenon), or known intermediate or poor metabolizer variant of the liver enzyme CYP2D6. Current use of any of the following known strong CYP2D6 inhibitors: fluoxetine (Prozac), paroxetine (Paxil), bupropion (Welbutrin), quinidine, quinine, ritonavir (Norvir), and terbinafine (Lamisil). Current use of the following other drugs known to pharmacodynamically interact with timolol: diltiazem, verapamil, digoxin, digitalis, propafenone, disopyramide, clonidine, flecainide, or lidocaine.\

Bevacizumab (Avestin)

Bevacizumab is an antibody directed against VEGF that is effective in cancer by stopping angiogenesis. VEGF levels are increased in the serum and nasal mucosa of HHT patients. Several case reports of HHT patients with cancer treated with bevacizumab for cancer showed marked improvement in bleeding and anemia.

Avastin 21 mg/ml in 15% Mucolaz #4 ml.
One spray each nostril BID
Should last 6 to 10 weeks

Mucolaz gel binder so drug doesn't run out of nose.

Compounded through: O'Brien Pharmacy
5453 W 61st Place Mission, Kansas 66205 1-800-627-4360

Thalidomide

Introduced in the 1950s to treat nausea in pregnancy. Removed from the market when a link between the drug and severe birth defects was noted. The cause of the birth defects is thought to be due to the antiangiogenic activity. The drug was re-instituted for the treatment of some cancers. It was observed that HHT-associated epistaxis among cancer patients improved when they were started on thalidomide. Studies suggest that thalidomide increases smooth muscle cell layers in blood vessels in the nasal mucosa. Based on 4 studies, thalidomide appears to [provide a significant improvement in the frequency, intensity, and duration of epistaxis. Patients may show benefit within one month will on the lowest dose (50 mg/daily). Patients should be started on lowest dose (50mg/d) with increase by 50 mg at 4 weeks, if minimal or no improvement. Intermittent dosing is possible.

Use in women of childbearing age must be avoided. Risk for thrombosis and presence of pulmonary AVMs. Peripheral neuropathy may occur in up to 10%; may resolve with lowering dose. However, peripheral neuropathy may not be reversible after cessation of thalidomide. Minor side effects include: drowsiness, dizziness, constipation, lethargy, and peripheral edema.

Dosing: 50 mg/d. Increase after 4 weeks only if response has not occurred in an attempt to avoid more serious side effects associated with higher doses. Max:150 mg QD.

Pomalidomide (Pomalyst)

Pomalidomide, a third-generation derivative of thalidomide, is an immunomodulator with antineoplastic and angiogenesis inhibitor activity and is used in the therapy of multiple myeloma. Pomalidomide is a member of the angiogenesis inhibitor class of drugs and is a thalidomide derivative and also structurally related to lenalidomide.

Pomalidomide for HHT-associated epistaxis is given orally at a starting dose of 4 mg/day for days 1-21 of a 28-day cycle indefinitely. The dose may be reduced to 3 or 2 mg/day based on specific AE criteria. Its use is restricted because of teratogenicity and strict adherence to birth control (for both men and women) is required. **Use in women of childbearing age must be avoided or associated with strict birth control measures.** The use of pamolidomide is associated with a low rate of serum aminotransferase elevations (liver injury) during therapy, which can be severe. Side effects of pomalidomide are common and similar to those of thalidomide and lenalidomide and include sedation, dizziness, orthostatic hypotension, neutropenia, thrombocytopenia, anemia, peripheral neuropathy and venous thromboembolism (for which reason it is usually given with antiplatelet agents such as aspirin or with anticoagulation). A Phase II placebo-controlled double-blind clinical trial (PATH-HHT) is currently being conducted at Cleveland Clinic by Dr. Keith McCrae (NCT03910244). The goal of the study is to determine efficacy of pomalidomide compared to placebo for the reduction in severity of epistaxis after 24 weeks of treatment.

Tacrolimus

Nasal ointment (Protopic)

Immunosuppressive drug; ointment Protopic topical therapy for atopic dermatitis
0.1% tacrolimus (Protopic) nasal ointment BID X 6 weeks

Oral (Prograf)

One mg QAM (dosage is based on weight, medical condition, blood test results - tacrolimus trough levels, and response to therapy. Large men may need an additional 0.5 mg QHS)
Ask hematologist to check tacrolimus trough level and Hgb/Hct/RBC levels Q 6 weeks and modify dosing accordingly. Side effects include: Shaking, headache, diarrhea, nausea/vomiting, upset stomach, loss of appetite, trouble sleeping, and tingling of the hands/feet may occur.

Etamsylate (Cyclonamine, Dicynene, **Dicynone,** Haemostop, Menostat)

Etamsylate is an antihemorrhagic agent, which is believed to work by increasing resistance in the endothelium of capillaries and promoting platelet adhesion. It also inhibits biosynthesis and action of those prostaglandins, which cause platelet disaggregation, vasodilation and increased capillary permeability. It has been shown to reduce bleeding time and blood loss from wounds. This appears to relate to increased platelet aggregation mediated by a thromboxane A2 or prostaglandin F2a-dependent mechanism. Etamsylate was also thought to stabilize capillaries, reinforcing capillary membranes by polymerizing hyaluronic acid.

Etamsylate limits capillary bleeding through its action on hyaluronic acid and initial studies showed a reduction in intraventricular hemorrhage.

Dosing: Two sprays each nostril once daily

125 mg/2 ml Dicynone

HHT-HOPE Clinical Trial - 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 hereditary hemorrhagic telangiectasia, during 4 weeks. Sponsored by the Asociación HHT España

https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-003982-24/ES#E

Future Medications

Pazopanib (Parambil)

Multikinase inhibitor that blocks new blood vessel growth. FDA-approved for treatment of cancers.

Dosing: 25 to 200 mg QD; 50 mg QD

Information in this handout from:

Halderman AA, Ryan MW, Clark C, et al. Medical treatment of epistaxis in hereditary hemorrhagic telangiectasia: an evidence-based review. *Int Forum Allergy Rhinol.* 2018;8(6):713-728.

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