Rare Diseases Clinical Research Network
Brain Vascular Malformation Consortium

Study Title: Topical Anti-angiogenic Therapy for Telangiectasia in HHT: Proof of Concept

Short Name: BVMC 6207

NCT# 01752049

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1.0 Protocol Synopsis

Protocol Number:	6207
Protocol Title:	Topical Anti-angiogenic Therapy for Telangiectasia in HHT: Proof of Concept
Study Chair:	Dr. Marie Faughnan
Statistician:	Dr. Charles McCulloch
Consortium:	Brain Vascular Malformation Consortium (BVMC)
Participating Sites:	St. Michael's Hospital (Toronto, Canada)
Sample Size:	10
Target Enrollment Period:	November 2012 to November 2015
Study Design:	Interventional, Double blind placebo-controlled trial
Primary Study Objective:	Our objective is to prove the concept that a topical anti-angiogenic therapy will lead to regression of vascular malformations in patients with Hereditary Hemorrhagic Telangiectasia (HHT).
Study Population and Main Eligibility/ Exclusion Criteria:	Study Population: 10 adult patients from St. Michael's Hospital who have Hereditary Hemorrhagic Telangiectasia (HHT) and have at least 5 typical telangiectasias on their hands or face Inclusion criteria: 1. Definite clinical or genetic diagnosis of HHT 2. Known ENG or ALK1 mutation (personal or familial) 3. Age ≥ 18 years 4. At least 5 typical (round/ovoid, not spider or linear) cutaneous telangiectasia (size range 2-5mm) on hands (not including lesions on over inter-phalangeal joints) or face Exclusion criteria: 1. Contraindication to systemic beta-blocker (severe asthma, severe COPD, sinus bradycardia, 2nd or 3rd degree AV block, overt heart failure, hypotension, allergy/intolerance/ hypersensitivity to timolol) 2. Current treatment with systemic beta-blocker 3. Current participation in other therapeutic trial for HHT 4. Current pregnancy or breastfeeding.
Treatment	
Agent:	Timolol Maleate Ophthalmic Solution USP 0.5%
Dosage, schedule, route of administration:	Topical timolol maleate 0.5% drops vs. placebo saline drops One drop applied twice daily for 12 weeks (84 days) or until disappearance of lesions. Study drops will be applied to 4 cutaneous telangiectasias per patient (timolol drops for 3 telangiectasia per patient and placebo drops to 1 telangiectasia per patient) using an eye dropper.
Safety Issues:	In clinical trials, Timolol maleate ophthalmic solution was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. Bradycardia was reported with timolol maleate ophthalmic solution. At trough (12 hours post-dose), the mean reduction was 3.6 beats/minute. At two hours post-dose, the mean reduction in heart rate was 5 beats/minute. Timolol maleate ophthalmic solution has also been used in patients with glaucoma wearing conventional hard contact lenses, and has generally been well tolerated.

Primary Outcome Measures:	Mean reduction in lesion area (compared with baseline measurement) of treated telangiectasia
Secondary Outcome Measures:	1. From Tissue: Descriptive changes in histopathology in baseline vs. treated lesions, vessel density and distribution of capillaries, arterioles and venules. 2. From speckle variance OCT: Changes in lesion area, blood flow velocity and volume flow rates (treated vs. baseline/ placebo). 3. Serum angiogenic markers (Aushon Blood-based Biomarkers in Clinical Research kit, analyzing 5- angiogenic biomarkers): Endoglin, BMP-9, VEGF+, TGF-beta1, TSP-1 at baseline and 84 days. 4. Stability of area of untreated telangiectasias over the 84 day period (placebo group)
Statistical Considerations (sample size and analysis plan):	This is a small proof of concept pilot study of 10 patients from St. Michael's Hospital who have Hereditary Hemorrhagic Telangiectasia (HHT) and have at least 5 typical telangiectasias on their hands or face, during a 3 month period. Standard descriptive statistics will be used for reporting primary and secondary outcomes. Reduction in telangiectasia area: Will analyze log area using a mixed linear regression model with predictors of time, treated/not and the interaction of time and treated/not (which compares the percent reduction in lesion area between treated and untreated lesions). The mixed model would include random effects for participant, lesion within participant and the change over time. Same analyses would be used for OCT variables.
Sponsors (federal, state, foundation and industry support):	National Institute of Health

1.1 Overview

Hereditary hemorrhagic telangiectasia (HHT) is a hereditary vascular condition characterized by the development of abnormal connections between arteries and veins throughout the body, called vascular malformations. These abnormal blood vessels are referred to as arteriovenous malformations (AVM) if they are large and telangiectasias if they are small.

Telangiectasias develop due to irregular growth of blood vessels. Anti-angiogenic therapy, such as the study medication Apo-timop, curbs the growth of new blood vessels. Apo-timop is included in a class of medications called beta-blockers. Anti-angiogenic therapies exert their beneficial effects in a number of ways: by disabling the agents that activate and promote cell growth, or by directly blocking the growing blood vessel cells.10 adults with Hereditary Hemorrhagic Telangiectasia (HHT) and have at least 5 typical telangiectasias on their hands or face from the Toronto HHT Centre at St. Michael's Hospital in Toronto, Canada will be eligible for this study.

The purpose of this study is to prove that using an anti-angiogenic therapy (a therapy that inhibits or prevents the growth of new blood vessels) will lead to a shrinkage of telangiectasis in HHT patients.

The research team has extensive experience in HHT in general (Marie Faughnan, Michelle Letarte, clinical research (Marie Faughnan, William Young), cutaneous HHT (Anne Curtis) and anti-angiogenic therapy (Michelle Letarte, Peter Kertes). Anne Curtis is a dermatologist with extensive expertise in HHT; she will collect tissue (perform the telangiectasia biopsies). Henry Jakubovic is a dermato-pathologist who will oversee tissue preparation and perform histopathology review. Victor X. D Yang is a biomedical engineering scientist with combined biophotonics research and neurosurgical training. He has a clinical interest in cerebral vascular diseases and experience using optical coherence tomography (OCT) in HHT cutaneous lesions [1], the only published experience of this type. Michelle Letarte is a leading basic scientist in mechanisms of disease in HHT.

We hope that this study will provide proof of this concept and might lead to the development and study of anti-angiogenic therapies to improve the lives of individuals with vascular malformations.

Topical timolol maleate 0.5% drops or placebo saline drops will be applied to 4 telangiectasias on the subjects' hand, twice daily for 12 weeks (84 days) or until disappearance of lesions (timolol drops for 3 telangiectasia per patient and placebo drops to 1 telangiectasia per patient).

2.0 Specific Aims (Hypothesis and Objectives)

Rationale:

The goal of the study is to demonstrate that an antiangiogenic agent can lead to regression of a vascular malformation in humans with HHT. To date the evidence for anti-angiogenic effectiveness in HHT remains largely in animal arteriovenous malformation (AVM) models. In humans, there are case reports and small case series showing improvement in complex clinical outcomes (severe chronic bleeding, heart failure) using systemic (intravenous) antiangiogenic therapy, without demonstrating regression of AVMs per se. Though this is promising and these are important clinical outcomes, the mechanism for the clinical improvement remains unknown and it remains uncertain whether antiangiogenic therapy can lead to AVM regression in human HHT.

The current study aims to address these unanswered questions by studying, in humans, lesions that are accessible to direct (topical) therapy, given their superficial skin location, and that are likely to be most responsive to therapy. We believe that skin telangiectasia are more likely to be responsive to therapy given that they are smaller, likely "earlier" vascular malformations, and more dynamic in patients. People with HHT develop new telangiectasia as they advance through life. The development of new (large) organ AVMs however, are rarely seen in adults with HHT. As such we have

chosen to treat skin telangiectasia in this study. Using a topical therapy also allows us to treat only the lesions and local surrounding tissues, therefore minimizing exposure to the drug, as compared to treating with a systemic agent.

The outcomes of this study should have two major implications. First, if the pilot study outcome is positive, then we propose to study timolol (and potentially other beta-blockers) as a systemic agent in a clinical trial to regress brain AVMs in HHT. Second, we can use this topical study design to test other agents of interest (bevacizumab, pazopanib, thalidomide derivatives, antioxidants, etc.) for regression of vascular malformations in HHT. If the study process and outcome measures are feasible, then this topical drug screening study design can be used for testing other agents, regardless of whether the pilot study outcome is positive. In addition, we plan to use results from the study of other future screened agents to guide clinical trials of these agents in brain AVMs in HHT.

Hypothesis: Topical anti-angiogenic therapy will lead to regression of cutaneous telangiectasia in patients with Hereditary Hemorrhagic Telangiectasia (HHT).

Specific Hypothesis: Topical timolol (beta-blocker) therapy will lead to regression of skin telangiectasia in patients with HHT.

3.0 Background

Telangiectasias develop due to dysregulated angiogenesis in patients with HHT. There is evidence in some HHT mouse models that anti-angiogenic therapy can lead to regression of experimental vascular malformations (VMs). In addition, there are case reports of chronic bleeding and VM-related shunting regressing in HHT patients treated with anti-angiogenic therapy for other indications. We expect that anti-angiogenic therapy will lead to regression of VMs in HHT patients, with the smallest VMs (telangiectasia) likely to be most responsive to therapy. We propose to prove this concept in easily accessible cutaneous telangiectasia by treating with a topical beta-blocker, with known anti-angiogenic properties. If the concept is proven, this may lead to new therapies for VMs in HHT and improvement in quality of life, morbidity (chronic bleeding, heart failure and stroke) and mortality.

HHT is due to mutations in endoglin (ENG; HHT1) or activin receptor-like kinase 1(ALK1 or ACVRL1; HHT2). These two genes code for receptors for BMP9 and TGF-beta, which are known to play a role in the regulation of angiogenesis. The underlying mechanism of HHT is haploinsufficiency, implying that it is the 50% reduction in the functional amount of these proteins that is responsible for disease initiation. This reduction in functional endoglin or ALK-1 predisposes vessels to stress such as increased blood flow, inflammation or injury, leading to vascular remodeling and VMs. While ALK-1 conditional knockout mice (cKO; where ALK1 is deleted in endothelial cells) develop VMs in multiple visceral organs, secondary insults like wounding are necessary to induce sub-dermal vessels to form de novo VMs. It was subsequently shown that either induction of inflammation or angiogenesis, using LPS or VEGF

respectively, could recapitulate the wound response and generate VMs. Treatment with neutralizing antibodies to VEGF led to significant blunting of both inflammation and angiogenesis and prevented wound-induced VMs[2].

Though interest is growing in the concept of anti-angiogenic therapy for HHT, there are no published controlled clinical trials of antiangiogenic therapies in HHT patients to date. There are however isolated case reports [3-5] and small series of reduced bleeding and shunting [6, 7] in HHT patients treated with either bevacizumab or thalidomide, both antiangiogenic therapies. In addition, there is an isolated case report of treatment with intranasal topical bevacizumab demonstrating regression of nasal telangiectasia[8, 9] and very recently an isolated case of nasal mucosal topical treatment with timolol with reported reduction in epistaxis in an HHT patient[10].

Recent clinical and cellular reports suggest that beta-blockers should also be considered as potential therapeutic agents given their anti-angiogenic properties. There are no published cases or studies to date of the use of beta-blockers therapy for HHT lesions, though there is growing case report[11] and small case series evidence[12-14] of effectiveness of topical beta-blocker in cases with other cutaneous VMs, such as infantile hemangiomas, in which these lesions regressed within weeks. Propanolol, a non-selective beta-adrenergic blocking drug, was recently shown to control the growth of hemangiomas. A recent study reported that propranolol inhibited the growth of endothelial cells in culture through G0/G1 cell cycle arrest; it also blocked the migration and differentiation of endothelial cells into capillary-like structures. Propanolol inhibited VEGF receptors downstream signaling, including MMP2 metallo-protease activation, which participates in vascular remodeling [15]. These data suggest that propranolol not only blocks adrenergic receptors but can interfere with VEGF receptor mediated pathways, therefore interfering with angiogenesis. A recent study indicated that propranolol was protective against retinal angiogenesis in an oxygen-induced mouse retinopathy model [16].

Our goal is to prove the concept that anti-angiogenic therapy in HHT can cause regression of VMs. Topical beta-blocker is a particularly interesting agent for this proof of concept pilot study, for a number of reasons. First, as noted above, there is some clinical evidence of effectiveness for regression of VMs in other disorders and there are plausible biological mechanisms. Second, it appears to be a low risk therapy. There is 50% bioavailability with mucosal application but cutaneous cases treated to date have had no systemic side effects (systemic bioavailability unknown with cutaneous application, though likely very low), and in these reported cases treatment area was much larger than we propose here. Third, the treatment is feasible in that it is available, inexpensive, easily applied topically, rapidly effective (days to weeks) allowing for a feasible study time line.

4.0 Study Design and Methods

Setting: Toronto HHT Centre, St Michael's Hospital Toronto Canada.

Design: Double blind placebo-controlled, with randomization of lesions for treatment versus placebo.

Randomization for assignment of telangiectasia: For each participant, the 5 telangiectasia will be numbered (1-5) and then randomly assigned to: biopsy, timolol_biopsy, timolol, timolol, placebo. The person measuring (mm measures and OCT) will remain blinded to the assignment.

4.1 Inclusion Criteria

1. Definite clinical or genetic diagnosis of HHT
2. Known ENG or ALK1 mutation (personal or familial)
3. Age>=18 years
4. At least 5 typical (round/ovoid, not spider or linear) cutaneous telangiectasia (size range 2-5mm) on hands (not including lesions on over inter-phalangeal joints) or face.

4.2 Exclusion Criteria

1. Contraindication to systemic beta-blocker (severe asthma, severe COPD, sinus bradycardia, 2nd or 3rd degree AV block, overt heart failure, hypotension, allergy/intolerance/ hypersensitivity to timolol)
2. Current treatment with systemic beta-blocker
3. Current participation in other therapeutic trial for HHT
4. Current pregnancy or breastfeeding.

4.3 Recruitment of Participants

Recruitment target: 10 patients.

The Toronto HHT Clinic at St. Michael's Hospital has approximately 300 patients who would meet inclusion criteria, of whom only approximately 10% would have exclusion criteria. Patients will be screened for eligibility from our St. Michael's Hospital HHT Database. Participants in our HHT Database have agreed to be screened and contacted for the studies for which they are eligible.

4.4 Retention Strategies

Subjects are seen or called weekly for monitoring and will be reminded of their next visit. At the baseline visit all visit dates are arranged.

4.5 Data Elements

Outcomes:

Primary: Mean reduction in lesion area (compared with baseline measurement) of treated telangiectasia.

Secondary:

1. From Tissue: Descriptive changes in histopathology in baseline vs treated lesions, vessel density and distribution of capillaries, arterioles and venules.

2. From speckle variance OCT: Changes in lesion area, blood flow velocity and volume flow rates (treated vs baseline/ placebo).

3. Serum angiogenic markers (Aushon Blood-based Biomarkers in Clinical Research kit, analyzing 5- angiogenic biomarkers): Endoglin, BMP-9, VEGF+, TGF-beta1, TSP-1 at baseline and 84 days.

4. Stability of area of untreated telangiectasias over the 84 day period (placebo group)

Measurements:

1. Data collection of eligibility information, demographics and concomitant medications

2. Telangiectasia size:
    a. Baseline measurement: with mm graded calipers, in largest diameter, of all 5 telangiectasia (targeted for treatment, placebo and tissue)
    b. Post-treatment/placebo (days #14, 28, 56, 84) measurement: with mm graded calipers, in largest diameter, for 4 telangiectasia (3 treated/1 placebo)

3. Speckle Variance Optical Coherence Tomography (OCT) Vasculature Measurements:
   A Fourier domain mode locking (FDML) swept source optical coherence tomography (SS-OCT) system is used to obtain the OCT measurements. This system uses a 43–67 kHz FDML fiber-ring laser source incorporating a polygon-based tunable filter with a sweeping range of 112 nm centered at 1310 nm, −6 dB ranging depth of 6 mm in air (corresponding to a coherence length of 12 mm), axial resolution of ~ 8 um in tissue, and average output power of 48 mW. The total cavity length used in FDML the laser ranges from 3.3 to 4.5 km. A fiber Bragg grating provides the A-scan trigger. Inter-frame speckle variance images of the structural OCT intensity are calculated across B-mode images. [17]
    a. Baseline measurements (Day #0) in all 5 telangiectasia: 3-dimensional structural (3mmx3mmx3mm), Doppler, and speckle variance OCT

(SVOCT) imaging[17]. Derived parameters include vascular volume, vessel diameter distribution, velocity and volume flow rate

b. Post-treatment/placebo (days #14, 28, 56, 84) measurement for 4 telangiectasia (3 treated/1 placebo): 3-dimensional structural, Doppler, and SVOCT imaging. Derived parameters include vascular volume, vessel diameter distribution, velocity and volume flow rate.

4. Tissue sampling:
   a. Baseline: Excisional 3mm punch biopsy of 1 cutaneous telangiectasia (day #0, untreated), after local injection with lidocaine-epineprhine.
   b. Post-treatment (at 50% reduction of one lesion or day #84, whichever comes first): Excisional 3mm punch biopsy of 1 timolol-treated cutaneous telangiectasia (randomly selected amongst timolol treated), after measurement, and after local injection with lidocaine-epineprhine
   c. Preparation: Tissue will be fixed in 10% buffered formalin and stained for H&E stain, PAS stain, smooth muscle cell actin and CD31. Four sections (slides) per sample will be prepared, using standard techniques.
   d. Tissue analysis: All measurements (vessel densities) will be reported as mean per section and reviewed by two independent pathologists.

4.6 Schedule of Events

	Baseline	**Day 14**	**Day 28**	**Day 56**	**Day 84**
Data collection (eligibility information, demographics)	x				
Data collection (concomitant medications)	x	x	x	x	x
Measurements (calipers)	x	x	x	x	x
Photos of 5 telangiectasias	x				
Photos of 4 treated telangiectasias					x
OCT	x	x	x	x	x
Urine Pregnancy Test	x				
Serum angiogenic markers	x				x
Resect (biopsy) telangiectasis that will not be treated	**± 3 days* x**				
Resect (biopsy) a randomly selected timolol treated telangiectasia					**± 3 days* x** (or at 50% size reduction)
Monitoring for adverse outcomes		x**	x	x	x

*Flexibility needed for booking biopsies

**In addition to weekly calls in between visits

5.0 Data and Safety Monitoring Plan

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) before submission to individual center IRB/REBs for approval. Participant enrollment may only begin with IRB/REB approved consent forms.

This is an interventional pilot study that meets the federal definition of low risk.

Monitoring for local adverse outcomes (rash, pain, bleeding of telangiectasia) and systemic adverse outcomes (hypotension, bradycardia, drowsiness, bronchospasm) by clinical assessment will occur at days #14, 28, 56, 84 and also by telephone contact weekly. Participants will also be able to reach a study coordinator or investigator if they have concerning symptoms at other times, by pager. If there are uncomfortable or concerning side effects, the study investigator will stop the study treatment and manage as medically appropriate.

Adverse events will be reported to Health Canada, St. Michael's Research Ethics Board, and the RDCRN. (See section 5.4 for more information on reporting responsibilities.)

The Study Chair will appoint an NINDS approved Independent Medical Monitor (IMM) to review all reported adverse events that are serious, unexpected, and possibly/probably/definitely related to the study intervention in real time.

The IMM will also review cumulative adverse events. The frequency of review of cumulative AEs will be determined by the IMM in conjunction with the Study Chair and will occur at least once every 12 months. The IMM will then evaluate whether the protocol or informed consent document requires revision based on the reports.

5.1 Study Oversight

The Study Chair has primary oversight responsibility of this clinical trial. The Brain Vascular Malformation Consortium will review accrual, patterns and frequencies of all adverse events, and protocol compliance at least every 6 months.

The site's Principal Investigator and her research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying adverse events. Aggregate report- detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures – will be available from the Rare Diseases Clinical Research Network (RDCRN) Data Management and Coordinating Center (DMCC) for site review. Adverse events will be reviewed weekly by the research team. A separate report detailing protocol compliance will also be available from the DMCC for site review on a monthly basis.

5.2 Definitions and Standards

The Rare Diseases Clinical Research Network defines an adverse event as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

An unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks of information described in the protocol.

Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute.

5.3 Expected/Known Risks/Discomforts/Adverse Events Associated with Study Intervention and Procedures: Definition of Expected Adverse Events

Timolol maleate ophthalmic solution (Apo-Timolol) is usually well tolerated when applied to the eye. As with many topically applied ophthalmic drugs, this drug is absorbed systemically when applied mucosally. Though systemic bioavailability is unknown with cutaneous application, it is likely very low. In addition, there has been no clinic evidence to date of systemic absorption in reported cutaneous treatment cases to date, and treatment area was much larger in these cases than we propose here. As this is a small pilot study and we have very limited resources, we will not attempt these assays until the next larger study.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical cutaneous administration. Possible risks and discomforts are detailed below; however, there may be other risks and side effects that are not yet known.

As this is a pilot study we are not aware of any risks associated with Apo-timop applied topically to the skin. Our goal is to prove the concept that anti-angiogenic therapy in HHT can cause regression of VMs. Topical beta-blocker is a particularly interesting agent for this proof of concept pilot study, for a number of reasons. First, as noted above, there is some clinical evidence of effectiveness for regression of VMs in other disorders and there are plausible biological mechanisms. Second, it appears to be a low risk therapy.

There is 50% bioavailability with mucosal application but cutaneous cases treated to date have had no systemic side effects (systemic bioavailability unknown with cutaneous application, though likely very low), and in these reported cases treatment area was much larger than we propose here.

The following sections are cited from the Product Monograph:

"WARNINGS AND PRECAUTIONS
General
As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. The same adverse reactions reported with systemic beta-adrenergic blocking agents may occur with topical administration. Timolol maleate ophthalmic solution should be used with caution in patients subject to spontaneous hypoglycemia or in diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol maleate has little or no effect on the pupil. When timolol maleate ophthalmic solution is used to reduce elevated intraocular pressure in angle-closure glaucoma they should be used with a miotic and not alone. Cardiac failure should be adequately controlled before beginning therapy with timolol maleate ophthalmic solution. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solutions. Because of the potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patient with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with timolol maleate ophthalmic solution, alternative therapy should be considered.
Endocrine and Metabolism
Thyrotoxicosis
β-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of β-adrenergic blocking agents which might precipitate a thyroid storm.
Immune
Risk from Anaphylactic Reaction
While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens,either accidental, diagnostic, or therapeutic. These patients may be more resistant to treatment of anaphylactic reactions with the usual doses of epinephrine since timolol may blunt the beta agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.
Ophthalmologic

Choroidal Detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide or combination) after filtration procedures. Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously. As with the use of other antiglaucoma drugs, diminished responsiveness to timolol maleate ophthalmic solution after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least 3 years, no significant difference in mean intra ocular pressure has been observed after initial stabilization.
Contact Lenses
The preservative in APO- TIMOP ophthalmic solution is benzalkonium chloride. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. Therefore, APO-TIMOP ophthalmic solution should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.
Neurologic
Muscle Weakness
β-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.
Peri-Operative Considerations
Major Surgery
The necessity or desirability of withdrawal of β-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic blocking agents. If necessary during surgery, the effects of β-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.
Special Populations
Pregnant Women:
Timolol maleate ophthalmic solution has not been studied in human pregnancy. The use of timolol maleate ophthalmic solution requires that the anticipated benefit be weighed against possible hazards.
Nursing Women:
Timolol is detectable in human milk. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatrics:
Safety and effectiveness in children have not been established."

Risks Related to Study Tests

Blood Sample Collection: When blood samples are taken from a vein, subjects may have discomfort or pain where the blood was taken. Sometimes a person may become dizzy or faint when blood is taken. There is also a risk of infection (rare), bleeding, redness or bruising at the skin puncture. Bleeding and bruising can usually be reduced by putting pressure on the place where the blood was taken. The chance of infection is lowered by using standard skin cleaning and sterile needles.

Optical Coherence Tomography (OCT): This test will take approximately 30 minutes at each visit. The light used is near infrared at safe power level (significantly below the American National Standards Institute exposure level). It will not cause heating or any sensation or any other known harmful effects. OCT has been used for imaging the human retina during clinical visits. During imaging the patient is required to remain still intermittently. There are no other inconvenience factors that we foresee.

Biopsy: Subjects will have to travel to the Dr. Curtis'office at Bloor and Avenue Road for this procedure. They will need to schedule an extra 2 hours at 2 visits. Transportation will be arranged and paid for. The needle with the freezing causes a stinging or burning sensation for a few seconds, until the freezing takes hold. There is no pain during the remainder of the biopsy, because the area is frozen. It is possible there may be bruising, which could last for 2 weeks. There is a small risk of a local skin infection. This can be treated with an antibiotic cream, or occasionally requires antibiotics by mouth. There is likely to be a small scar at the site of the biopsy, which will be red initially, and will fade to pale over a few months to a year. It is much less common to have a raised itchy scar, which could be injected with cortisone to help it flatten.

5.4 Reporting Timeline

- Within **24 hours** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:
  - Is considered life-threatening/disabling or results in death of subject

  -OR-
  - Is Unexpected/Unanticipated
- Investigators must report all other reportable SAEs within **5 working days** (of learning of the event).
- All other (suspected) reportable AEs must be reported to the RDCRN within **20 working days** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.5 RDCRN Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event, the DMCC created Adverse Event Data Management System (AEDAMS) will immediately notify the Study Chair, site PIs, the IMM, and any additional agencies (if applicable- industry sponsor, CTEP, etc.) of any reported adverse events via email.

Serious adverse events: The IMM determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event. A back-up notification system is in place so that any delays in review by the IMM beyond a specified period of time are forwarded to a secondary reviewer. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his/her research team will be submitted to the DMCC in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the IMM on a bi-annual basis. Local site investigator is also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all reported adverse events for site investigators and IRB/REBs.

5.6 Study Discontinuation

The NIH and local IRB/REBs (at their local site) have the authority to stop or suspend this trial at any time. This study may be suspended or closed if:

- Accrual has been met
- The study objectives have been met
- The Study Chair / Study Investigators believe it is not safe for the study to continue
- The NIH suspends or closes the trial
- The FDA suspends or closes the trial

5.7 Subject Discontinuation

An intent to treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent. Every effort will be made to conduct a final study visit with the participant and participants will be followed clinically until, if applicable, all adverse events resolve.

- Withdrawal of consent
- Withdrawal by the participant

- Withdrawal by the investigator due to the subject's intolerance to timolol or non-compliance
- Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease (e.g.-mental status change, large pleural effusion).

5.8 Data Quality and Monitoring Measures

- Data Monitoring: The research coordinator will identify missing or unclear data and generates a data query to the research team.
- Data Delinquency Tracking: The research coordinator will monitor data delinquency on an ongoing basis.

5.9 Quality Control: Study Related Procedures

An extra patient will be recruited as a "lead-in" (or test run) phase for the OCT imaging and comparison of telangiectasia size caliper measurement, without drug administration or tissue sampling. The study chair presumes only one test patient will be sufficient. If this patient is eligible and willing to participate in the BVMC 6207 Research Study, the patient would be consented for the BVMC 6207 Research Study and the results of the test run imaging may be used for the BVMC 6207 Research Study.

6.0 Statistical Considerations

This is a small proof of concept pilot study of 10 patients from St. Michael's Hospital who have Hereditary Hemorrhagic Telangiectasia (HHT) and have at least 5 typical telangiectasias on their hands or face, during a 3 month period.

Sample Size: There is no justification for sample size. This is a small pilot study. If we can detect any effect then we will plan a future larger study, based on the results of this pilot.

Standard descriptive statistics will be used for reporting primary and secondary outcomes.

Reduction in telangiectasia area:
We will analyze log area using a mixed linear regression model with predictors of time, treated/not and the interaction of time and treated/not (which compares the percent reduction in lesion area between treated and untreated lesions). The mixed model would include random effects for participant, lesion within participant and the change over time. Same analyses would be used for OCT variables.

Definition of a significant reduction in lesion size:
We have defined a successful outcome of therapy (a "go" decision) based on considering both clinical and statistical significance, as has been previously suggested [18] and to balance error rates. If there is a statistically significant improvement in

lesion size at the usual level (α=0.05, one-sided test) or if there is a clinically important improvement (at least a 20% reduction in lesion size) as well as borderline statistical significance (α=0.10, one-sided test) we will consider this a successful outcome for timolol.

7.0 Data Management

Tissue samples will be analyzed and reviewed at St. Michael's Hospital. Blood samples will be sent to Aushon for Serum angiogenic markers. All results will be sent back to the research coordinators at St. Michael's Hospital and will be entered into the 6207 data spreadsheets. Data will be stored on a password protected computer in a locked room using unique identifiers. Identifying log will be kept separate from data at St. Michael's Hospital. De-identified data on spreadsheets will be sent to UCSF for analysis. The data will be electronically sent using encrypted communication links. Demographics data will be transferred to the DMCC monthly and all outcomes data will be transferred to the DMCC at the end of the study.

All data will also be uploaded from site to DMCC by secure file transfer process (SFTP).

All study data at the RDCRN Data Management and Coordinating Center will comply with all applicable guidelines regarding patient confidentiality and data integrity.

7.1 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the participant is registered to participate in the study, using the DMCC provided web-based registration system, the system will assign a participant ID number. Thus each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant. In this fashion, no personal identifiers would be accessible to the DMCC.

7.2 Data Entry

Tissue samples will be analyzed and reviewed at St. Michael's Hospital. Blood samples will be sent to Aushon for Serum angiogenic markers. All results will be sent back to the research coordinators at St. Michael's Hospital and will be entered into the 6207 data spreadsheets. Data will be uploaded from site to DMCC by secure file transfer process (SFTP).

8.0 Human Subjects

8.1. GCP Statement

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

8.2. Risks

Timolol maleate ophthalmic solution (Apo-Timolol) is usually well tolerated when applied to the eye. As with many topically applied ophthalmic drugs, this drug is absorbed systemically when applied mucosally. Though systemic bioavailability is unknown with cutaneous application, it is likely very low. In addition, there has been no clinic evidence to date of systemic absorption in reported cutaneous treatment cases to date, and treatment area was much larger in these cases than we propose here. As this is a small pilot study and we have very limited resources, we will not attempt these assays until the next larger study.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical cutaneous administration. Possible risks and discomforts are detailed below; however, there may be other risks and side effects that are not yet known.

As this is a pilot study we are not aware of any risks associated with Apo-timop applied topically to the skin. Our goal is to prove the concept that anti-angiogenic therapy in HHT can cause regression of VMs. Topical beta-blocker is a particularly interesting agent for this proof of concept pilot study, for a number of reasons. First, as noted above, there is some clinical evidence of effectiveness for regression of VMs in other disorders and there are plausible biological mechanisms. Second, it appears to be a low risk therapy.

There is 50% bioavailability with mucosal application but cutaneous cases treated to date have had no systemic side effects (systemic bioavailability unknown with cutaneous application, though likely very low), and in these reported cases treatment area was much larger than we propose here.

The following sections are cited from the Product Monograph attached to this submission:

"WARNINGS AND PRECAUTIONS

General

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. The same adverse reactions reported with systemic beta-adrenergic blocking agents may occur with topical administration. Timolol maleate ophthalmic solution should be used with caution in patients subject to spontaneous hypoglycemia or in diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia. In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol maleate has little or no effect on the pupil. When timolol maleate ophthalmic solution is used to reduce elevated intraocular pressure in angle-closure glaucoma they should be used with a miotic and not alone. Cardiac failure should be adequately controlled before beginning therapy with timolol maleate ophthalmic solution. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solutions. Because of the potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patient with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with timolol maleate ophthalmic solution, alternative therapy should be considered.

Endocrine and Metabolism

Thyrotoxicosis

β-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of β-adrenergic blocking agents which might precipitate a thyroid storm.

Immune

Risk from Anaphylactic Reaction

While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens,either accidental, diagnostic, or therapeutic. These patients may be more resistant to treatment of anaphylactic reactions with the usual doses of epinephrine since timolol may blunt the beta agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.

Ophthalmologic

Choroidal Detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide or combination) after filtration procedures. Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously. As with the use of other antiglaucoma drugs, diminished responsiveness to timolol maleate ophthalmic solution after prolonged therapy has been

reported in some patients. However, in clinical studies in which 164 patients have been followed for at least 3 years, no significant difference in mean intra ocular pressure has been observed after initial stabilization.

Contact Lenses

The preservative in APO- TIMOP ophthalmic solution is benzalkonium chloride. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. Therefore, APO-TIMOP ophthalmic solution should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

Neurologic

Muscle Weakness

β-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Peri-Operative Considerations

Major Surgery

The necessity or desirability of withdrawal of β-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic blocking agents. If necessary during surgery, the effects of β-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Special Populations

Pregnant Women:

Timolol maleate ophthalmic solution has not been studied in human pregnancy. The use of timolol maleate ophthalmic solution requires that the anticipated benefit be weighed against possible hazards.

Nursing Women:

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics:

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. Timolol maleate ophthalmic solution is usually well

tolerated. The following adverse reactions have been reported with ocular administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed.

Body as a Whole

Headache, asthenia, fatigue, chest pain.

Cardiovascular

Aggravation or precipitation of certain cardiovascular pulmonary and other disorders presumably related to effects of systemic beta blockade has been reported (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS). These include bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, palpitation, cardiac arrest, congestive heart failure, edema, claudication, Raynaud's phenomenon, cold hands and feet and in insulin-dependent diabetics masked symptoms of hypoglycemia have been reported rarely. Nausea, diarrhea, dyspepsia, dry mouth.

Hypersensitivity

Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localized and generalized rash.

Immunologic

Systemic lupus erythematosus.

Integumentary

Alopecia, psoriasiform rash or exacerbation of psoriasis.

Nervous System/Psychiatric

Dizziness, depression, insomnia, nightmares, memory loss, increase in signs and symptoms of myasthenia gravis, paresthesia.

Respiratory

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, cough.

Special Senses

Signs and symptoms of ocular irritation: including burning and stinging, conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity, and dry eyes. Visual disturbances: including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, and choroidal detachment following filtration surgery (see WARNINGS AND PRECAUTIONS). Tinnitus.

Urogential

Decreased libido, Peyronie's disease.

Causal Relationship Unknown

The following adverse reactions have been reported but a causal relationship to therapy with timolol maleate ophthalmic solution has not been established: aphakic cystoid macular edema, nasal congestion, anorexia, CNS effects (e.g., behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances), hypertension, retroperitoneal fibrosis and pseudopemphigoid.

Potential Adverse Reactions

Adverse reactions reported in clinical experience with systemic timolol maleate may be considered potential side effects of ophthalmic timolol maleate."

Risks Related to Study Tests

Blood Sample Collection: When blood samples are taken from a vein, subjects may have discomfort or pain where the blood was taken. Sometimes a person may become dizzy or faint when blood is taken. There is also a risk of infection (rare), bleeding, redness or bruising at the skin puncture. Bleeding and bruising can usually be reduced by putting pressure on the place where the blood was taken. The chance of infection is lowered by using standard skin cleaning and sterile needles.

Optical Coherence Tomography (OCT)

This test will take approximately 30 minutes at each visit.
Subjects will travel by taxi to and from Sunnybrook Hospital for OCT imaging.
This could amount to 1-2 extra hours due to travelling time.
The light used is near infrared at safe power level (significantly below the American National Standards Institute exposure level). It will not cause heating or any sensation or any other known harmful effects. OCT has been used for imaging the human retina during clinical visits. During imaging the patient is required to remain still intermittently. There are no other inconvenience factors that we foresee.

Biopsy

Subjects will have to travel to the Bloor and Avenue Road for this procedure. They will need to schedule an extra 2 hours at 2 visits. Transportation will be arranged and paid for.The needle with the freezing causes a stinging or burning sensation for a few seconds, until the freezing takes hold. There is no pain during the remainder of the biopsy, because the area is frozen. It is possible there may be bruising, which could last for 2 weeks. There is a small risk of a local skin infection. This can be treated with an antibiotic cream, or occasionally requires antibiotics by mouth. There is likely to be a small scar at the site of the biopsy, which will be red initially, and will fade to pale over a few months to a year. It is much less common to have a raised itchy scar, which could be injected with cortisone to help it flatten. Subjects may opt not to include telangiectasia located on their face if they so prefer to avoid facial scarring or the palms of their hands as it may be somewhat more painful.

8.3 Benefits

Subjects will not benefit directly from inclusion in this study. However, we hope that at the end of this pilot study, researchers will be in a better position to propose therapies and studies that may help reduce vascular malformations in individuals with HHT.

8.4 Recruitment

Approximately 300 HHT Database cases will be reviewed for eligibility. Subjects enrolled in our HHT Database have consented to be screened for study eligibility. All eligible patients will be approached: there will be no internal bias. There is no proposed exclusion of any sex/gender or racial/ethnic group.

8.5 Written Informed Consent

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

8.6 Process of Consent

Contact will be made by phone or in clinic by the research coordinator who is usually familiar with her/him from being recruited for the database. In most cases the treating physician (PI) would mention the patient's potential eligibility for the study and ask if delegated staff could contact them. However all patients have shown research interest by consenting to be on our HHT Database.

<u>Obtaining Informed Consent:</u>

Patient is approached in Clinic or by phone.

- Study Coordinator (RC) will explain the information of the written informed consent to the patient.
- Patient will be asked several times if he/she understood details of the study and if he or she has questions about it.
- Patient will be offered extra time to read, consider discuss the study.
- If participant would like more time to think about his/her participation he/she will be offered an unsigned consent form to take home and study and a plan will be made for a follow-up conversation in clinic or by phone.
- Patient will be asked if he/she would agree to participate in this study.
- Patient will sign informed consent in clinic before starting any study procedures.
- Patient will receive a signed copy of consent.

If patient does not consent to having this conversation he/she will be thanked for their time.

In all cases, patients will be given as much time as they like to make their decision.

9.0 References

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Statistical Considerations

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