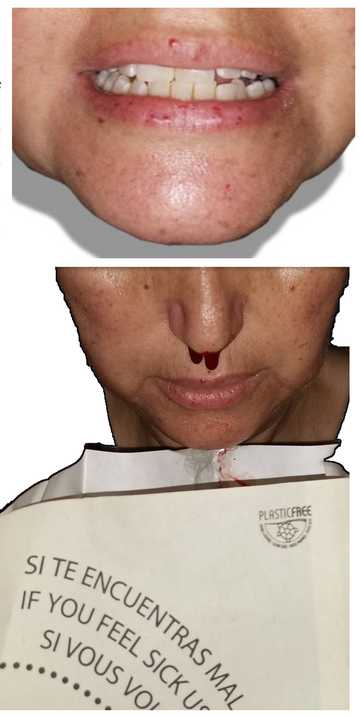
ANTIANGIOGENIC TREATMENT FOR HEREDITARY HAEMORRHAGIC TELANGIECTASIA

Author: Rubén Olivares Torres
Tutor: José Martín Quintana Aguiar
Co-tutor: Francisco Jesús Estévez Rosas

WHAT IS HHT

In 2000 and after different consensus it was classified by the Diagnostic Cruraçao Criteria for the high prevalence in Curaçao Island (1:1331). In the criteria specify the frequent signs and defining of this: spontaneous and recurrent epistaxis, multiple telangiectases in characteristic sites, hereditary pattern, and specific visceral lesions. The Curaçao agreement defines as a positive a diagnostic in people who suffers three of four symptoms, or two of them with a genetic confirmation test of HHT.



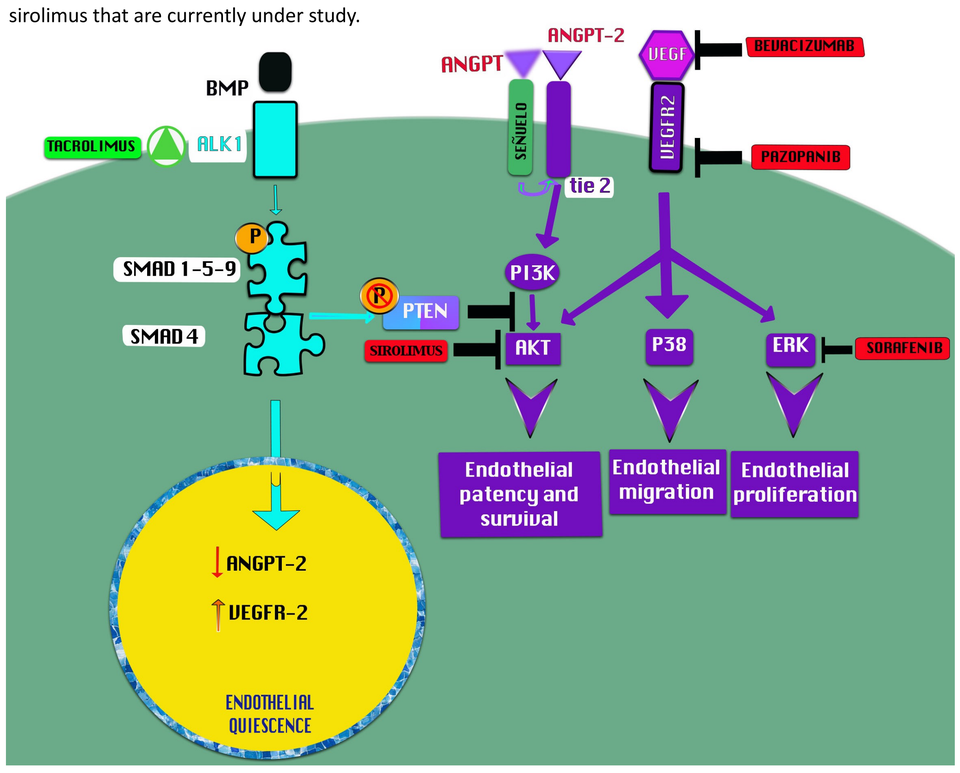
Curaçao Criteria

The HHT diagnosis is

Definite	if 3 criteria are present
Possible or suspected	if 2 criteria are present
Unlikely	if fewer than 2 criteria are present
1. Epistaxis	spontaneous, recurrent nose bleeds
2. Talangiectases	multiple, at characteristic sites: • Lips • Fingers • Oral cavity • Nose
3. Visceral lesions	such as: • Gastrointestinal telangiectasia (with or without bleeding) • Pulmonary AVM • Hepatic AVM • Cerebral AVMs • Spinal AVM
4. Family history	a final degree relative with HHT according to these criteria

SIGNAL TRANSDUCTION

The antiangiogenic drugs, involved in vascular dysplastic diseases such as HHT, were designed to stop tumour growth, blocking its proliferation capacity avoiding the formation of new vessels. Among there are antiVEGF antibodies like bevacizumab and inhibitors of VEGF receptors with tyrosine kinase activity like pazopanib. On the other hand, sirolimus or sorafenib are inhibitors of later stages. Biological therapies activators of ALK1, that are not angiogenesis inhibitors, but promoters of endothelial quiescence, like tacrolimus and sirolimus that are currently under study.



METHODOLOGY

STRATEGY SEARCH: “Drug X” + “hereditary haemorrhagic telangiectasia”.

Bevacizumab strategy: 137
Tacrolimus strategy: 7
Sorafenib strategy: 1
Sirolimus strategy: 4
Pazopanib strategy: 4

Filter:
Randomized or not
clinical trials

144 studies discarded

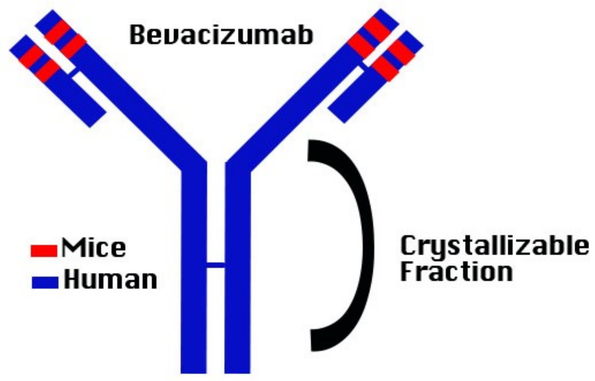
bevacizumab: 6
tacrolimus: 1
sorafenib: 0
sirolimus: 1 ✖
pazopanib: 1

Clinical trial of sirolimus in mice discarded

GLOSSARY

ACVLR1 – Activin receptor-like kinase 1 gene
AKT – Protein kinase B
ALK1 – Activin receptor-like kinase 1
ANGPT – Angiopoietin
BAD – BCL2 associated agonist of cell death
BMP – Bone morphogenic protein
BMPR2 – Bone morphogenic protein receptor 2
ENG – Endoglin gene
ERK – Extracellular signals regulate kinase
ESS – Epistaxis Severe Score
FcRn – Neonatal Fc receptor
HHT – Hereditary haemorrhagic telangiectasia
MAPK – Mitogen-activated protein kinase
MAV – Arteriovenous malformations
mTOR – mechanistic target of rapamycin
PI3K – Phosphatidylinositol 3-kinases
PTEN – Phosphatase and tensin homolog
SMAD – Family of proteins homologues to small worm phenotypes and MAD drosophila
TGF – Transforming growth factor
TIE2 – Angiopoietin receptor
VAS – Visual analogue score
VEGF – Vascular endothelial growth factor
VEGFR2 – Vascular endothelial growth factor receptor

BEVACIZUMAB



Bevacizumab is a humanized recombinant monoclonal antibody from mice, administered intravenously with a molecular weight like immunoglobulins. The crystallizable fraction binds to epithelial cells for difussion. It has been developed using hybridoma technology, extracting mouse lymphocytes B in response to human VEGF immunization and mixing them with human myeloma cell lines to develop hybrid antibodies. The result is an antibody with 97% of the aminoacidic sequence of the human and 7% of the mice.

CLINICAL TRIALS WITH ANTIANGIOGENIC TREATMENT IN HHT

Reference	Treatment	Dose	N	Results	Efficace
Dupuis-Girod et al.[32] (2012)	Bevacizumab IV.	5 mg/kg every 2 weeks for 12 weeks (6 doses)	24	↑Heart index: 5,02 L/min/m² beginning 4,2 L/min/m² 3 months ↓Epistaxis duration: 221 min/month beginning 134 min/month 3 months 43 min/month 6 months	p < 0,001 p = 0,008
Dupuis-Girod et al.[33] (2014)	Bevacizumab topic intranasal	12,5-25-50-75-100 mg/mL Five groups (1:1)	80	≈Tolerability to treatm.	Not measure
Riss et al.[34] (2015)	Bevacizumab Intranasal submucose	100 mg single dose	15	↓ESS: 3,9 (beginning) 2,9 (3 months) ↓Epistaxis duration: 6,2 min/day (beginning) 5,9 min/day (3 months)	p = 0,34 p = 0,86
Dupuis-Girod et al.[27] (2016)	Bevacizumab topic intranasal	25-50-75 mg/mL (increase in 3 groups) 3 sprays/week every 14 days (3 doses)	80	≈Epistaxis duration: Group 25mg – 259 min/month Group 50mg – 244 min/month Group 75mg – 215 min/month	p = 0,57
Whitehead et al.[35] (2016)	Bevacizumab topic intranasal vs other treatment	4 mg/day every 2 weeks for 12 weeks	120	↓Epistaxis dur. and freq. ↓ESS treatment and placebo.	p = 0,97 p < 0,01 Clinical but not statistical signif.
Chavan et al.[36] (2017)	Bevacizumab IV.	5 mg/kg every 2 weeks for 12 weeks (6 doses)	21	↑Heart index: 8,7 L/min/m² beginning 6,5 L/min/m² 3 months ↓ESS: 2,4 (beginning) 0,9 (3 months) ↑Hb: 10,8 g/dL beginning 12,6 g/dL 3 months	p < 0,0008 p < 0,0001 p < 0,0002
Faughnan et al.[24] (2019)	Pazopanib oral	50 mg/day	7	↓Epistaxis dur. and freq.: ≥ 50% 3 months ↑Hb: 2 g/dL ↓ESS ↑QoL	Clinical but not statistical significance
Dupuis-Girod et al.[37] (2020)	Tacrolimus topic ointment	0,1 g in 2 diary applications for 6 weeks	50	↓Epistaxis duration: 324 min/month begin 245 min/month after 6 w.	p = 0,77 end p = 0,04 during

ABSTRACT

Hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease) is an autosomal dominant and rare disease with a prevalence of 1:5000, with multisystemic vascular involvement. The vascular endothelial growth factor (VEGF) deficit produces an aberrant formation or arteriovenous malformations (AVM), derive from different identified mutations that produce different types of HHT. Type 1 is due to a mutation in *ENG* gene which affects endoglin biosynthesis, and type 2 is due for a mutation in *ACVRL1* gene which affects activin receptor-like protein kinase biosynthesis (ALK -1). Anti-angiogenic antibodies such as bevacizumab are used in the treatment of severe anaemias due to complex nosebleeds that are difficult to control with applicable results. These have established basis for new treatments that are beginning to be studied and appear promising.

DISCUSSION

Bevacizumab, when administered intravenously, it reduces severe recurrent epistaxis and corrects heart output due to secondary decompensation in patients with severe liver impairment, and also it was useful in the treatment of heart failure and the improvement of chronic anaemia. In a selecting cohort of patients with severe liver malformations and their consequent systemic decompensation the result was statistically significant, achieving recovery of the same previous parameters and reducing the need to receive liver transplants in many treated. Topical bevacizumab studies reach the same conclusion, symptoms such as epistaxis are not improved compared to placebo or other treatments such as tranexamic acid and oestrogens, and a single submucosal dose can be administered directly to the nasal septum, with results of relative reduction of epistaxis according to the VAS. In addition, this use of bevacizumab has been questioned due to the possibility of perforation of the septum during administration, as well as necrosis of the nasal wall because of the administration of a high dose of the antiangiogenic.

With pazopanib percentage improvements were obtained in the severity, duration, and frequency of epistaxis, as well as associated systemic parameters such as haemoglobin, the need for transfusions and an overall improvement in quality of life, but the results collected were not statistically relevant. The tacrolimus is useful because changes the endothelial quiescence previously explained but is not the one that offers better adherence to treatment by the patient since it consists of applying an ointment with a swab topically inside the nostrils, but relevant improvements have been obtained during the study process. The epistaxis reduced their duration with statistical significance in the monitoring during the study, but at the end of the study the reduction did

CONCLUSION

A rare disease is a dark reality for who suffers it. Physicians are not prepared to diagnose it due to its low prevalence. When they have a diagnostic it isn´t a good new because they suffer a rare disease, and, therefore, little studied, with limited treatments and in the best of cases, it will be limiting but not lethal in short term, like the case of HHT, it rarely produces haemorrhagic ictus or lethal digestive bleedings in short term. It is tremendously disabling to suffer a disease of this magnitude, that day by day weakens and depletes psychologically performing any action of daily life. Many organisms act for the visibility to thousands of existing rare diseases, that makes possible to find ways to study treatments like bevacizumab, finding relief and improvement for those with HHT. It is always necessary to elaborate further studies, better designed and with bigger samples, but it is difficult when the prevalence is so low. Also there are exclusively animal and in vitro studies, with the inhibitor of PI3K and MAPK like sirolimus or sorafenib respectively, and in an early future, it will be possible to extend to humans that will allow new therapeutic alternatives against rare diseases without effective treatments, similar to genetic technologies (CRISPR), these will can be an effective tool to fix genes with a DNA mapping, if we find answer to the ethic limits around these alternatives.

ANKOWLEDGMENTS

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