Pediatric Dermatology: Vascular Tumors and Malformations

Joan Tamburro, DO
Section Head of Pediatric Dermatology

Cleveland Clinic
Disclosures

- No financial disclosures
- Will discuss off label use of medications
- I never wanted to be a dermatologist … only a pediatric dermatologist
One additional disclosure

- Gratitude for the many people who have contributed to my professional career in providing my the ability to provide care to children and educate others so they can do the same.
Visionary

“Our field of study is subspecializing”

- 1998 – AOCD provided funding for a pediatric dermatology fellowship with the Medical College of Wisconsin under the leadership of Nancy Esterly, MD
- From 2004 till 2012 – Osteopathic Dermatology residency director at University Hospital, Cleveland Ohio
- In 2014 we completed the first CAQ in pediatric dermatology and continue to offer this CAQ
Lecture Overview

- Update on infantile hemangiomas
  - For the here and now
- Update on vascular malformations
  - A look into the future
Let’s start with the here and now
“New kids on the block”
“Or not so new kids on the block”
Objectives

- Review recent literature concerning infantile hemangiomas as it pertains to treatment
- Review the types if infantile hemangiomas that require treatment
- Compare propranolol to atenolol
- Discuss advantages of atenolol
- Review new advances in capillary, venous, lymphatic and arteriovenous malformations
We have come so far...
a walk down BAD memory lane
Luckily now ... we have a GOOD memory lane
Recent literature

- Pathogenesis
- Type of cells involved
  - Immature endothelial cells
  - Endothelial progenitor cells
  - Interstitial cells
  - Pericytes
  - Hemangioma derived stem cells

Recent literature

- **Molecular mechanisms**
  - Vasoconstriction
    - Beta receptors blocked by propanolol inhibit vasodilation by adrenaline and cause vasoconstriction
  - Inhibition of angiogenesis
    - By blocking the beta adrenoreceptors the ERK/MAPK is deactivated decreasing the release of VEGF
  - Induction of apoptosis
    - By disengaging the inhibition of apoptosis caused by beta-adrenergic agonists

Molecular processes in infantile hemangioma that may be affected by HEMANGEOL™

Adapted from Storch CH, Hoeger PH. British Journal of Dermatology. 2010;163:269-274.
Why treat

- More than one-half of children with untreated hemangiomas experience residual changes such as scarring, atrophy, redundant skin, discoloration, and telangiectasias
- “it will go away” … often not true

Now how do we take this “hammer” and use it well

- Use it early
- Use it wisely, not every infantile hemangioma needs to be treated
- Be detailed in expected goals
- As always …how can we use it locally and not as a systemic medication
Use it early

- Proliferative Phase
  - Much earlier than previously believed – the Iphone camera and anxious parents can not be disputed
  - Rapid growth is prior to 8 weeks of life
  - The time between their first pediatric appointment and the second

Gap in medical knowledge

- Use of beta blockers for infantile hemangiomas in 5 week and younger neonates
- Blood brain barrier in neonates
- Predicting growth of infantile hemangiomas
What IH need to be treated?

- Stratifying risks
- Prognosticating growth
- Weeks of life to evaluate
Risk Stratification

- **Very High Risk**
  - Segmental face or perineal
  - PHACE, PELVIS
- **High Risk**
  - Bulky lesions face
  - Central face
  - Periorbital, oral and nasal
  - Early white discoloration
Risk Stratification

- Moderate Risk
  - lateral face, scalp, hands and feet
  - Body folds
  - Segmental > 5 cm of trunk or extremities

- Low risk
  - Nonvisible areas

Very High Risk
Very High Risk
High Risk
High Risk
High Risk
High Risk
Moderate Risk
Moderate Risk
Low Risk
Propranolol

- First designed medication completed in 1964 by James Black
- Original goal was a treatment for angina, but also proves to be an antihypertensive
- Lipophilic non selective beta antagonist
- 2008 Dr. Leaute-Labreze publishes the first report of propanolol as treatment for infantile hemangiomas
- March 2014 FDA approves Hemangiol for IH treatment being initiated in 5 week
Propranolol dosing

- 0.6mg/kg/dose bid x 1 week
- Then increase to 1.1 mg/kg/dose bid x 1 week
- Then 1.7 mg/kg/dose bid ongoing
- Doses are at least 9 hours apart
- Treat for 6 months
- Monitor heart rate and blood pressure for 2 hours after initial dose and when increasing dose
Propranolol Contraindications

- Premature infants with corrected age < 5 weeks
- Infants weighing less than 2 kg
- Known hypersensitivity to propranolol or any of the excipients
- Asthma or history of bronchospasm
- Heart rate < 80 beats per minute, greater than first degree heart block, or decompensated heart failure
- Blood pressure < 50/30 mmHg
- Pheochromocytoma
Side Effects of Propranolol

- Nonselective β-blockers can block catecholamine-induced glycogenolysis, gluconeogenesis, and lipolysis, predisposing to hypoglycemia.

- Bronchial hyper-reactivity, described as wheezing, bronchospasm, or exacerbation of asthma/bronchitis, is a recognized side effect of propranolol as the result of its direct blockade of adrenergic bronchodilation.
Side Effects

- Hyperkalemia (without electrocardiographic changes) was reported in 2 children on propranolol for IH postulate that it was tumor lysis from the large ulcerated IH combined with impaired potassium uptake into cells as the result of β blockade.

- Dental caries have been reported in 2 pediatric patients treated with propranolol β-adrenergic antagonism of salivary gland function resulting in decreased salivation.
More Common Side Effects

- hypotension
- hypoglycemia
- sleep disturbance
- somnolence
- Diarrhea

Pediatrics. January 2013, VOLUME 131 / ISSUE 1
<table>
<thead>
<tr>
<th>Complications Recorded</th>
<th>No. of Patients/ Total No. of Patients in Papers Reporting Complication</th>
<th>Frequency (%) of Complication Among Papers Reporting Said Complication</th>
<th>Overall Frequency (%) of Total of 1175 Patients Reviewed in 85 Papers</th>
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<tbody>
<tr>
<td>Asymptomatic hypotension or hypotension (unspecified)</td>
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<td>2.8</td>
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<td>Symptomatic hypotension</td>
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<td>0.3</td>
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<td>Pulmonary symptoms (bronchoconstriction, bronchiolitis, wheezing, pulmonary obstruction, apneic episode)</td>
<td>16/201</td>
<td>8.0</td>
<td>1.4</td>
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<td>Hypoglycemia</td>
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<td>11.4</td>
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<td>Symptomatic bradycardia</td>
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<td>50</td>
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<td>Sleep disturbance (including nightmares)</td>
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<td>13.5</td>
<td>3.7</td>
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<tr>
<td>Somnolence</td>
<td>26/220</td>
<td>11.8</td>
<td>2.2</td>
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<tr>
<td>Cool or mottled extremities</td>
<td>20/225</td>
<td>8.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9/53</td>
<td>17.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease or gastrointestinal upset</td>
<td>8/133</td>
<td>6.0</td>
<td>0.7</td>
</tr>
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</table>
Atenolol

- Discovered in 1976
- Hydrophilic selective beta 1 antagonist
- Decrease chance of passing through blood brain barrier
- Decrease pulmonary effects
- Decrease chance of lowering endogenous catecholamines which can correct hypoglycemia
SCAMP

- Standardized clinical assessment and management plan
- Protocol to utilize when initiating a non-FDA approved medication. This protocol was reviewed and agreed upon by the Cleveland Clinic - Vascular Anomalies Team

Atenolol SCAMP

- ECG, HR, BP (MRI and MRA/ECHO for PHACES and PELVIS)
- Baseline heart rate and blood pressure
- Initiate 0.25 mg/kg and two and four hour post dose repeat HR and BP
- If tolerated send home on 0.25 mg/kg/dose bid
- After 1 week increase to 0.5 mg/kg/dose bid and keep that dose to follow up in 6-8 weeks
- If pt is greater than 6 months and ≥ 6.5 kg may go to qday dosing
- Try to wean starting at 12 to 15 months
Side Effects

- **Propanolol**
  - Hypotension
  - Pulmonary symptoms
  - Hypoglycemia
  - Bradycardia
  - Sleep disturbance
  - Somnolence
  - Diarrhea
  - GERD
  - Blue extremities

- **Atenolol**
  - Hypotension
  - Sleep disturbance
  - Constipation
  - Diarrhea
  - Mild side effects
    - 40% (50%)
  - Severe side effects
    - 3% (25%)

deGraaf et al. JPRASurg 2013;66,1732-1740
Treatment gaps in knowledge

- Treatment questions unanswered
  - Hypotension due to beta blockers and when there are associated congenital heart defects (coarctation of aorta) and neck vessel malformations
  - Regrowth after typical treatment – past 18 months of life
Could a topical beta blocker be as effective?

- Limit side effects
- Depth of absorption
- Application to skin with increased vascular spaces
- Evaluating treatment efficacy is very difficult, especially for deep and mixed
Topical timolol

- All patients except one improved, with a mean improvement of 45 ± 29.5%. Predictors of better response were superficial type of hemangioma (p = 0.01), 0.5% timolol concentration (p = 0.01), and duration of use longer than 3 months (p = 0.04).

Timolol seems to be a well-tolerated, safe treatment option with moderate to good effectiveness, demonstrating best response in thin, superficial IHs regardless of pretreatment size. Timolol can be recommended as an alternative to systemic β-blockers and watchful waiting for many patients.

Topical Timolol Studies

  - No significant response difference between topical timolol and oral propranolol

  - Timolol solution equals timolol gel forming solution

  - Timolol solution had less variability in the amount dispensed per 5 drops

  - Concern to use in patients less than 2500 gms and less than 44 weeks postmenstrual age
Take Home Points

- Use it early –
  - Use pediatric dermatology, pediatrician, pediatric cardiology
  - Should timolol be considered

- Use it wisely, not every infantile hemangioma needs to be treated
  - Use the risk stratification

- Be detailed in expected goals
  - Not growing, preventing ulceration, preventing need for surgery
Take Home Points

- Decide what stage the infantile hemangioma is in

- Risk Stratify
  - Risk for PHACE or PELVIS
  - Very high to moderate – propranolol/atenolol

- Low Risk
  - Full term or over 44 weeks PMA - topical timolol

- No need for treatment
Take Home Points

- Timolol dosing
- one drop of the timolol equals 0.05 ml
- concentration of topical timolol gel forming solution is 0.5% = 0.25 mg of timolol/drop.
- recommended daily dosage is less than 0.25 mg/kg
- the maximum safe daily dose of timolol is 1 drop per kilogram of body weight

In the Pipeline

- 8 NIH studies for infantile hemangiomas
  - % of topical timolol – 0.25% vs 0.5%
  - Topical propranolol
  - Nadolol vs propranolol
  - Atenolol vs propranolol
Over half way through
A look into the future
Our ability to discuss the medical treatment of vascular malformations is due to our recent advances in genetics, especially as it relates to mosaic genetic disorders.

... the “genes” are the answer.
Vascular Malformations

- Capillary Malformations
  - GNAQ

- Venous Malformations
  - PIK3CA

- Lymphatic Malformations
  - PIK3CA

- Arteriovenous Malformations
  - RASA1
Etiology and Genetics of Congenital Vascular Lesions

Angela Queisser, PhD, Laurence M. Boon, MD, PhD, Miikka Vikkula, MD, PhD
# ISSVA Classification for Vascular Anomalies

## Simple Vascular Malformations I

### Capillary Malformations (CM)
- Nevus simplex / salmon patch, “angel kiss”, “stork bite”
- Cutaneous and/or mucosal CM (also known as “port-wine” stain)
  - Nonsyndromic CM
  - CM with CNS and/or ocular anomalies (Sturge-Weber syndrome)
  - CM with bone and/or soft tissues overgrowth
  - Diffuse CM with overgrowth (DCMO)
- Reticulate CM
  - CM of MIC-CAP (microcephaly-capillary malformation)
  - CM of MCAP (megalencephaly-capillary malformation-polymicrogyria)
- CM of CM-AVM
- Cutis marmorata telangiectatica congenita (CMTC)
- Others

### Telangiectasia*
- Hereditary hemorrhagic telangiectasia (HHT) *(HHT1 ENG, HHT2 ACVRL1, HHT3, JPH3 SMAD4)*
- Others
ISSVA classification for vascular anomalies

**Simple vascular malformations I**

**Capillary malformations (CM)**

- Nevus simplex / salmon patch, “angel kiss”, “stork bite”
- Cutaneous and/or mucosal CM (also known as “port-wine” stain)
  - Nonsyndromic CM
  - CM with CNS and/or ocular anomalies (Sturge-Weber syndrome)
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<thead>
<tr>
<th>GNAQ</th>
<th>STAMBPEH</th>
<th>PIK3CA / RASA1 / EPHB4</th>
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### Simple vascular malformations III

<table>
<thead>
<tr>
<th>Venous malformations (VM)</th>
<th>TEK (TIE2) / PIK3CA</th>
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<tbody>
<tr>
<td>Common VM</td>
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<tr>
<td>Familial VM cutaneo-mucosal (VMCM)</td>
<td>TEK (TIE2)</td>
</tr>
<tr>
<td>Blue rubber bleb nevus (Bean) syndrome VM</td>
<td>TEK (TIE2)</td>
</tr>
<tr>
<td>Glomuvenous malformation (GVM)</td>
<td>Glomulin</td>
</tr>
<tr>
<td>Cerebral cavernous malformation (CCM)</td>
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<tr>
<td>(CCM1 KRI1, CCM2 Malcavernin, CCM3 PDCD10)</td>
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<tr>
<td>Familial intraosseous vascular malformation (VMOS)</td>
<td>ELMO2</td>
</tr>
<tr>
<td>Verrucous venous malformation (formerly verrucous hemangioma)</td>
<td>MAP3K3</td>
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<td>Others</td>
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## ISSVA classification for vascular anomalies

### Simple vascular malformations III

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Gene(s)</th>
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<tr>
<td>Venous malformations (VM)</td>
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<tr>
<td>Common VM</td>
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<tr>
<td>VMOS</td>
<td>ELMO2</td>
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<tr>
<td>Formerly verrucous hemangioma</td>
<td>MAP3K3</td>
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### ISSVA classification for vascular anomalies

#### Simple vascular malformations IIa

<table>
<thead>
<tr>
<th>Lymphatic malformations (LM)</th>
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<tbody>
<tr>
<td>Common (cystic) LM *</td>
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<tr>
<td>Macrocystic LM</td>
<td></td>
</tr>
<tr>
<td>Microcystic LM</td>
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</tr>
<tr>
<td>Mixed cystic LM</td>
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</tr>
<tr>
<td>Generalized lymphatic anomaly (GLA)</td>
<td>PIK3CA</td>
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<tr>
<td>Kaposiform lymphangiomatosis (KLA)</td>
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<tr>
<td>LM in Gorham-Stout disease</td>
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<tr>
<td>Channel type LM</td>
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<tr>
<td>“Acquired” progressive lymphatic anomaly (so called acquired progressive &quot;lymphangioma&quot;)</td>
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<tr>
<td>Primary lymphedema (different types)</td>
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<tr>
<td>Others</td>
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### ISSVA classification for vascular anomalies

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## ISSVA classification for vascular anomalies

### Simple vascular malformations IV

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<tr>
<th>Arteriovenous malformations (AVM)</th>
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<td>Sporadic</td>
<td>MAP2K1</td>
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<tr>
<td>In HHT</td>
<td>(HHT1 ENG, HHT2 ACVRL1, HHT3, JPHT SMAD4)</td>
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<tr>
<td>In CM-AVM</td>
<td>RASA1 / EPHB4</td>
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<tr>
<td>Others</td>
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<table>
<thead>
<tr>
<th>Arteriovenous fistula (AVF) (congenital)</th>
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</tr>
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<tbody>
<tr>
<td>Sporadic</td>
<td>MAP2K1</td>
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<tr>
<td>In HHT</td>
<td>(HHT1 ENG, HHT2 ACVRL1, HHT3, JPHT SMAD4)</td>
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<td>In CM-AVM</td>
<td>RASA1 / EPHB4</td>
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<td>Others</td>
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## ISSVA classification for vascular anomalies

### Simple vascular malformations IV

**Arteriovenous malformations (AVM)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Genes/Tissue</th>
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<td>Sporadic</td>
<td>MAP2K1</td>
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<tr>
<td>In HHT</td>
<td>(HHT1 ENG, HHT2 ACVRL1, HHT3, JPHT SMAD4)</td>
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<tr>
<td>BF (congenital)</td>
<td>MAP2K1</td>
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<tr>
<td></td>
<td>(HHT1 ENG, HHT2 ACVRL1, HHT3, JPHT SMAD4)</td>
</tr>
<tr>
<td></td>
<td>RASA1 / EPHB4</td>
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</table>
Capillary Malformation

- GNAQ Arg 183
  somatic mosaic mutation in *GNAQ* that causes Sturge–Weber syndrome and isolated port-wine birthmarks

  This gene defect will stop the cell from going to an inactive state leading to the proliferative endothelial cells.
Capillary malformation – treatment research studies

- Sirolimus – most studied
- Brimonidines – topical alpha 2 adrenergic agonist
- Timolol – beta blocker topical
- Taloporfirn – intravenous photosensitizer photodynamic therapy
Sirolimus

- First discovered on Easter Island it is produced by a bacteria Named after native island Rapa Nui (rapamycin)
- Original development was for fungal infections
- FDA approved the use for immunosuppression in 1999
Sirolimus

- mechanism of action of sirolimus is to bind the cytosolic protein FK-binding protein 12 (FKBP12). sirolimus-FKBP12 complex inhibits the mTOR (mammalian Target Of Rapamycin, rapamycin being another name for sirolimus) pathway by directly binding to mTOR Complex 1 (mTORC1).

- mTORC1 controls protein synthesis
Venous/Lymphatic Malformation

- PIK3CA
  - Found with venous malformations and overgrowth vascular malformations
    - Klippel Trenaunay and CLOVES
Venous/Lymphatic Malformations

- PIK3CA gene provides instructions for making the p110 alpha (p110α) protein, which is one subunit of the enzyme phosphatidylinositol 3-kinase (PI3K).
  - p110α protein is called the catalytic subunit because it performs the action of PI3K while the other subunit (produced by a different gene) regulates the enzyme's activity.
Venous/Lymphatic Malformations

- PI3K phosphorylates certain signaling molecules, which triggers a series of additional reactions that transmit chemical signals within cells.
- PI3K signaling is important for many cell activities, including cell growth and division (proliferation), movement (migration) of cells, production of new proteins, transport of materials within cells, and cell survival.
Venous/Lymphatic Malformations – treatment research

- Sirolimus

- Medical therapy alone
  - Hand full of patients with improvement, but more so when the lesion is venolymphatic

- Surgical and medical
  - Medical therapy in combination with sclerotherapy and/or surgery
Lymphatic Malformations - research studies

- Sirolimus
  - Similar mechanism of action for capillary malformations and venous malformations
Lymphatic Malformations - research studies

- Propranolol for lymphatic malformations
  - Retrospective case series review
  - 6 patients – including a fetus of a mother treated from 35 weeks gestation and on
Arteriovenous Malformations

- The RASA1 gene provides instructions for making a protein - p120-RasGAP. This protein helps regulate the RAS/MAPK signaling pathway, which transmits signals from outside the cell to the cell's nucleus.
- This protein directs several important cell functions, including the growth and division of cells, differentiation and cell movement.
Arteriovenous Malformations

- p120-RasGAP protein is a negative regulator of the RAS/MAPK signaling pathway, it is involved in turning off these signals when they are not needed.
- The exact role of p120-RasGAP is not fully understood, but is essential for the normal development of the vascular system.
Arteriovenous Malformations

- **RASA1**
  - **Sirolimus**
    - Similar mechanism of action as capillary, venous and lymphatic malformation
  - **Bevacizumab** – 5 mg/kg q 2 weeks for 12 weeks
    - a recombinant humanized *monoclonal antibody* that blocks angiogenesis by inhibiting *vascular endothelial growth factor A* (VEGF-A). VEGF-A is a growth factor protein that stimulates angiogenesis in a variety of diseases
Bevacizumab

- originally derived from a mouse monoclonal antibody generated from mice immunized with the 165-residue form of recombinant human VEGF

- humanized by retaining the binding region and replacing the rest with a human full light chain and a human truncated IgG1 heavy chain,
Bevacizumab

- approved in 2004, for combination use with standard chemotherapy for metastatic colon cancer. It has since been approved for use in certain lung cancers, renal cancers, ovarian cancers, and glioblastoma multiforme of the brain.
In the pipeline

- Topical sirolimus (rapamycin)
  - Used on various vascular malformations
  - Most effective for lymphatic malformations
Take Home Points

- Surgical and sclerotherapy for vascular malformations have been the main and only therapeutic option for years

- With the recent advances in genetic discoveries and how they pertain to vascular malformations, hopefully we will have many new medical therapies

- In the present, for complicated high risk vascular anomalies utilizing medical therapies may lessen the patient’s morbidity
Thanks