Treating Vascular Malformations in the Face, Head and Neck Using Trametinib

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SUMMARY STATEMENT

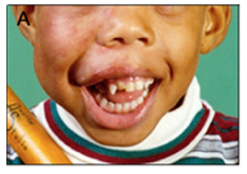
Treating extracranial arteriovenous malformations (AVM) with the FDA-approved cancer drug trametinib in pediatric patients who have failed other treatments

DISEASE/CONDITION

Extracranial arteriovenous malformation (AVM) is a network of abnormal blood vessels in the face, head or neck, which can cause tissue overgrowth, pain, ulceration, disfigurement and functional impairment.

Children with AVM usually need repeated high-risk surgical interventions throughout their lives, which are associated with complications including:

- bleeding/pain
- end organ damage
- surgical site complications
- cardiac failure



The cost of interventions and repeat hospitalizations have significant economic implications in healthcare and can create a financial burden for families.

CURRENT TREATMENT

Currently, there is no FDA approved medical treatment for this debilitating condition.

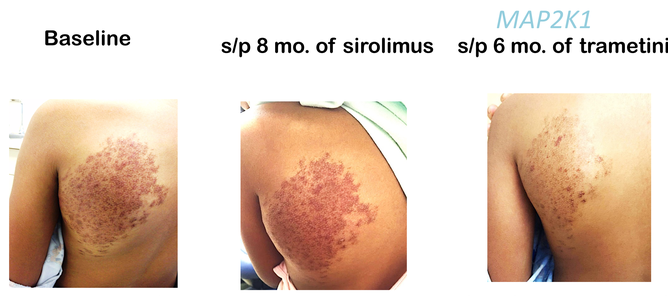
Treatments such as surgical debulking and interventional radiologic procedures are often reserved for those with severe end organ dysfunction. In addition, they only result in transient benefits to a small number of patients, as more than 50% to 90% cases recur within a year.

PROPOSED TREATMENT

Repurposing trametinib, a treatment for advanced melanoma, in AVM may provide an easily accessible therapeutic, potentially resulting in improved clinical status, quality of life and survival.

Extracranial AVM is a disorder that results from genetic mutations most commonly affecting *MAP2K1* gene, which codes for proteins involved in Ras/MAPK signaling. A previous study has shown that inhibitors of MEK, which is downstream of Ras/MAPK signaling, are effective in the treatment of AVM in experimental models.

Trametinib is a MEK inhibitor and is FDA approved to treat melanoma. Our preliminary case report using trametinib in a 10-year-old girl with a rapidly progressing AVM due to a *MAP2K1* mutation showed an excellent clinical response after six months and exhibited only mild acne as a side-effect.



Fig, 1: Case report showing AVM treatment response with sirolimus or trametinib

Based on results from our case study and recent discoveries, we hypothesize that treating complex AVM pediatric patients (defined as those who have failed previous therapies or exhibited complications) with trametinib will prove to be safe and effective, resulting in improved clinical status, quality of life and survival.

PROJECT

A non-blinded, single-arm pilot study to examine the impact of trametinib in slowing disease progression and improving the overall quality of life for extracranial AVM patients.

The study will enroll 21 patients at Stanford University Hospital / Stanford Children's Health, Boston Children's Hospital, the Children's Hospital of Philadelphia and the University of California, San Francisco. Patients will be over 13 years of age with clinical and radiologically confirmed diagnosis of AVM and will receive oral trametinib daily in continuous 28-day cycles for up to twelve months.

Specific Aims

- To determine the safety and efficacy of trametinib in treating complicated AVM
- To determine the disease response to treatment
- To correlate therapeutic responses with changes in biomarkers of AVM

The successful repurposing of trametinib may allow physicians to manage this disease before it progresses to more advanced stages. For patients with extensive diseases, this therapy also offers a possible adjuvant treatment to reduce the frequency and risks of surgical interventions and stabilize disease progression.

In addition, results from this study will hopefully pave the way to repurpose targeted medical treatments for many other complex vascular anomalies.

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