Sirolimus for cerebral cavernous malformation treatment

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Sirolimus and its use for cerebral cavernous malformation treatment (CCMs) is a subject of ongoing research and clinical trials, and it's considered an experimental therapy for this condition.

Sirolimus has attracted attention as a potential treatment for CCMs due to its anti-angiogenic (anti-blood vessel formation) properties and its potential to reduce inflammation in the blood vessels. Here are a few important points to consider regarding sirolimus for CCM treatment:

Experimental Treatment: The use of sirolimus for CCMs is experimental and not yet established as a standard of care. Clinical trials are ongoing to evaluate its safety and effectiveness.

Research and Clinical Trials: Researchers are conducting studies to assess whether sirolimus can reduce the growth of CCMs, decrease the risk of bleeding, or improve neurological outcomes for individuals with CCMs.

Patient Eligibility: If sirolimus is being considered as a treatment option, it is typically reserved for individuals with symptomatic CCMs who may not be suitable candidates for surgery or for whom surgery carries significant risks.

Risks and Side Effects: Sirolimus has potential side effects, including immunosuppression, which can increase the risk of infections, and metabolic effects, such as elevated cholesterol levels. The benefits and risks of using sirolimus must be carefully weighed for each patient.

Multidisciplinary Care: CCM management often involves a multidisciplinary team of healthcare providers, including neurologists, neurosurgeons, and interventional radiologists. Sirolimus treatment, if considered, is typically part of a comprehensive care plan.

It's important to emphasize that the use of sirolimus or any other experimental treatment for cerebral cavernous malformations should be done under the supervision of qualified medical professionals and in the context of a clinical trial or with informed consent, considering the potential risks and benefits. Treatment decisions for CCMs should be tailored to the individual's unique medical history and circumstances.

Li et al. developed a model of CCM formation that closely reproduces key events in human CCM formation through inducible CCM loss-of-function and PIK3CA gain-of-function in mature mice. In the present study, they used this model to test the ability of rapamycin, a clinically approved inhibitor of the PI3K effector mTORC1, to treat rapidly growing CCMs.

They show that both intraperitoneal and oral administration of rapamycin arrests CCM growth reduces perilesional iron deposition, and improves vascular perfusion within CCMs.

The findings further establish this adult CCM model as a valuable preclinical model and support clinical testing of rapamycin to treat rapidly growing human CCMs [1].

LoPresti et al. performed a descriptive retrospective cohort study examining pediatric patients genetically screened through the Pediatric Neurovascular Program of a single treatment center. Patients 18 years of age and younger with neurovascular anomalies, diagnosed radiographically or histopathologically, were evaluated for germline genetic testing. Patient demographic data and germline genetic testing and recommendation, clinical, treatment, and outcome data were collected and analyzed.

Sixty patients were included; 29 (47.5%) were female. The mean age at consultation was 11.0 ± 4.9 years. Diagnoses included cerebral arteriovenous malformations (AVMs) (n = 23), cerebral cavernous malformations (n = 19), non-neurofibromatosis/non-sickle cell moyamoya (n = 8), diffuse cerebral proliferative angiopathy, and megalencephaly-capillary malformation. Of the 56 patients recommended to have genetic testing, 40 completed it. Genetic alterations were found in 13 (23%) patients. Four patients with AVMs had RASA1, GDF2, and ACVRL1 mutations. Four patients with cavernous malformations had Krit1 mutations. One with moyamoya disease had an RNF213 mutation. Three patients with megalencephaly-capillary malformation had PIK3CA mutations, and 1 patient with a cavernous sinus lesion had a MED12 mutation. The majority of AVM patients were treated surgically. Patients with diffuse cerebral proliferative angiopathy were treated medically with sirolimus. At-risk relatives of 3 patients positive for genetic anomalies had also been tested.

Conclusions: This study demonstrates a role in exploring genetic alterations in the identification and treatment of pediatric neurovascular disease pathogenesis. Germline genetic mutations were found in almost one-quarter of the patients screened in this study, results that helped to identify medically targeted treatment modalities for some pediatric neurovascular patients. Insight into the genetic etiology of vascular anomalies may provide broader clinical implications for risk assessment, family screening, follow-up surveillance, and medical management [2].

Ren et al. demonstrated that cerebral cavernous malformation (CCM) growth requires increased PI3K/AKT/mTOR pathway and loss of CCM protein function. They identified PIK3CA gain of function (GOF) and CCM loss of function (LOF) somatic mutations in the same cells in a majority of human CCMs. Using mouse models, they showed that CCM growth requires both PI3K GOF and CCM LOF in endothelial cells, and that both CCM LOF and increased expression of the transcription factor KLF4, a downstream MEKK3 effector, augment mTOR signalling in endothelial cells. Consistent with these findings, the mTORC1 inhibitor Rapamycin effectively blocks CCM formation in mouse models. They established a three-hit mechanism analogous to cancer in which aggressive vascular malformations arise through the loss of vascular “suppressor genes” that constrain vessel growth and gain of a vascular “oncogene” that stimulates excess vessel growth. These findings suggest that aggressive CCMs may be treated using clinically approved mTORC1 inhibitors [3].

1)
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2)
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