

Rapamycin as Novel Treatment for Refractory-to-Standard-Care Slow-Flow Vascular Malformations

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Background: Venous and lymphatic malformations are composed of ectatic veins with scarce smooth muscle cell coverage, and of lymphatic cysts, respectively. They often cause deformity, pain, local intravascular coagulopathy or chronic infection. Despite sclerotherapy and/or excision, lesions often recur. Targeted pharmacological therapies are not available.

Purpose : To assess the efficacy and security of Rapamycin, an mTor inhibitor, which targets the disease-causing, activated PI3K-AKT signaling pathway, on children and adults affected with difficult-to-treat microcystic lymphatic malformations (LMs), extended venous malformations (VMs) and/or complex slow-flow vascular anomalies, which are no more amenable to conventional management.

Methods : Informed consent was obtained and approved by our ethical committee. The trial is registered under VASCA-LM at clinicaltrials.gov (NCT01811667). Eighteen patients aged from 3 to 64 years with refractory-to-standard-care LMs (n=6), VMs (n=7) and/or complex vascular anomalies (n=5) were enrolled. Clinical symptoms included: chronic daily debilitating pain (n=12), functional impairment (n=9), recurrent infections (n=5), daily gastrointestinal bleeding (n=4), and chronic ulceration with oozing and bleeding (n=2), despite several sessions of sclerotherapies and/or surgery. Patients were seen on a monthly basis by the plastic surgeon and the oncologist. Efficacy was evaluated by anamnesis of symptoms (functional, cosmetic and psychological), pain evolution (frequency and intensity), quality of life questionnaire, clinical parameters, photos of the visible clinical lesions and blood sampling. A global self-evaluation percentage of increase/decrease in quality of life (including social and physical function, vitality, and pain) was recorded at each follow-up as well as side effects. Volumetric MRI using ITK-SNAP software was performed before initiation and at a yearly base.

Results : Fifteen patients reached 12 months follow-up. All but one patient experienced almost complete relief of pain and symptoms, improved functional restraint and self-perceived quality of life under Rapamycin medication. Side effects were minor. Importantly, a statistically significant reduction in volume was also observed, with MRIs showing a decrease in most patients that reached one-year follow-up.

Conclusion : Results from this clinical trial suggest that Rapamycin can be a possible therapeutic option for patients with signs and symptoms of refractory-to-standard-care LMs, VMs and/or complex slow-flow vascular anomalies. However, as Rapamycin is likely a life-long treatment with side effects, it should not be considered as treatment for small, localized and asymptomatic slow-flow vascular malformations that respond to standard care.