Single centre experience of Sirolimus therapy in head and neck low-flow vascular malformations

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Abstract

Objective

Recently, studies have shown that sirolimus is clinically efficacious in the treatment of some low-flow vascular malformations (LFVM). This study aimed to assess the efficacy and safety of sirolimus in treating complex head and neck (H&N) LFVM that were challenging and/or refractory to standard treatment.

Methods

Each patient had baseline and six-months assessments consisting of clinical history and examination, quality of life (QoL) questionnaires, laboratory investigations, MRI and medical photography. Patients were followed up one-week and then one-monthly for six-months. Wilcoxon signed-rank test was used to compare pre- and six-months treatment in all eight domains of RAND 36-Item Short Form Health Survey (SF-36), hospital anxiety and depression scale (HADS), and visual analogue score for pain (VAS-P). $P<0.05$ was considered significant.

Results

Seven patients (median age 43 years, range 23-65 years) were recruited. Six patients completed the six-months course of therapy with one patient withdrawing due to intolerable side effects. All six patients reported reduction of swelling with and without other symptom improvement related to the vascular malformations whilst on treatment. However, at one-month review after discontinuation of sirolimus, five patients reported return of initial symptoms. Overall, patients demonstrated an improvement in QoL six-months treatment but there was no statistical significance ($P>0.05$) in all eight domains of SF-36, HADS and VAS-P. Five patients demonstrated a minimum 10% decrease in

lesion size six-months treatment (median 21%, range 13-40%). A Wilcoxon signed-rank test showed that sirolimus treatment did elicit a statistically significant change in lesion size in either direction (Z = -1.992, P = 0.046). The most common side effects found were dyslipidaemia (n-4) and mouth ulcers (n=2).

Conclusion

In our preliminary experience, sirolimus is effective and safe in treating patients with complex H&N LFVM. This provides an alternative treatment where standard treatment is challenging and/or refractory.

Keywords

Vascular malformations, Complex vascular malformation, Head and neck, Sirolimus, mTOR inhibitors

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Introduction

Congenital vascular malformations occur during early vascular development, resulting in abnormally formed vessels. These lesions can be broadly divided into low-flow and high-flow vascular malformations .The former refers to lesions with no arterial components which can be further characterized by their predominant endothelial cell type: capillary, lymphatic, venous, or any combination of them. The latter are lesions composed of arteries and veins that directly communicate through a central nidus without an intervening capillary bed.[1] The incidence of low-flow vascular malformation is approximately 1 in 10 000[2], of which venous malformation is the most common type with a prevalence of 1% of the general population.[3] Venous malformations can present anywhere in the body. They are most frequently found in the head and neck; constituting about 40% of all venous malfomations.[4] The mainstay interventional treatment for low-flow malformations include sclerotherapy and open surgical excision.[5,6] Both interventions carry potential risks including bleeding, infection, thromboembolism, end-organ ischaemia, poor wound healing, ulcer and nerve injury. Extensive head and neck low-flow vascular malformations present additional challenges for interventional procedures due to their complex anatomy of the vital structures including the airway, orbits, oropharynx, and cranial nerves.[7]

Mammalian target of rapamycin (mTOR) is a serine threonine kinase regulated by phosphoinositide-3-kinase (PI3K) and Akt. The PI3K/Akt/mTOR pathway plays an important role in cellular proliferation, adhesion, migration, invasion, metabolism and survival.[8] Vascular endothelial growth factor (VEGF) is an important regulator of

angiogenesis and acts as an upstream stimulator and downstream effector in mTOR signalling.[9-11] It is of no surprise therefore that mTOR inhibitors have been investigated as a treatment option in patients with complex vascular anomalies.[11] Inhibiting mTOR will consequently prevent downstream protein synthesis, cell proliferation and angiogenesis.[12] Sirolimus, an mTOR inhibitor, has demonstrated efficacy in the treatment of complicated vascular anomalies and patients that are refractory to standard care; particularly those with low-flow vascular malformations.[13] The use of sirolimus as an anti-angiogenetic was first reported in a child with refractory Kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon.[14] This was based on the tumour's lymphatic component and activation of the PI3K/Akt/mTOR pathway in angiogenesis and lymphangiogenesis.[11] With the shown early benefit of sirolimus in the literature,[15] we aimed to trial a six-months course medical treatment in complex head and neck non-central nervous system low-flow vascular malformations that were challenging and/or refractory to standard treatment to measure both its efficacy and safety profile in a multidisciplinary vascular anomalies specialist centre.

Methods

This study was an audit of prospective case series of patients with complex head and neck low-flow vascular malformations receiving sirolimus treatment in a single specialist centre. Sirolimus was an approved medical treatment within our vascular malformation service by the local drug and therapeutics committee with regular audit to assess its clinical efficacy and safety profile, hence no additional research ethics approval was required. All patients received verbal counselling and written patient information leaflet for sirolimus treatment, and informed consent from patients were obtained for this trial.

Patient recruitment

All patients with head and neck low-flow vascular malformations who presented to our vascular anomaly specialist clinic from March 1st, 2018 to November 1st, 2018 were assessed by a multi-disciplinary team (MDT) approach, consisting of vascular surgeons, interventional radiologists and clinical nurse specialist, for eligibility for sirolimus treatment.

Inclusion criteria:

- Symptomatic and confirmed head and neck low-flow vascular malformations on clinical assessment and radiological scans including duplex ultrasonography, computed tomography (CT) and/or magnetic resonance imaging (MRI), that were deemed too high risk, contraindicated and/or refractory to interventional therapy (sclerotherapy and/or surgery) by the MDT. Examples of these cases include those with deep, extensive and/or diffuse lesions, involving or in close proximity to vital head and neck structures such as the airways and major nerves, predominantly microcystic or capillary lesions, and/or limited success from previous interventional treatments .
- Male and female of age 18 years or above

Exclusion criteria:

- Contra-indications to sirolimus (e.g. allergy)
- Non-head and neck low-flow vascular malformations
- Central nervous system involvement
- Patient who does not consent to sirolimus treatment
- Patient who had concurrent interventional treatment for vascular malformations such as sclerotherapy and/or surgery during the sirolimus treatment period

Study protocol

Figure 1 summarises the treatment pathway of a patient commencing on sirolimus

Pre-treatment

At least one-week prior to commencing sirolimus each patient was assessed with the followings as the baseline:

- Clinical history taking and examination including for their demography, and symptoms and signs
- Quality of life (QoL) questionnaires; RAND 36-Item Short Form Health Survey (SF-36), hospital anxiety and depression scale (HADS), and visual analogue score for pain (VAS-P).
- Laboratory blood tests; full blood count (FBC), urea and electrolytes, liver function test, and serum lipid profile
- MRI of the head and neck
- Medical photography of the head and neck

Day of commencing treatment

All patients were reviewed in the out-patient clinic on the day they were prescribed, hence commenced on sirolimus treatment to ensure complete and satisfactory baseline assessments, and to address any remaining patients' concern. Oral sirolimus (Rapamune, Gilead) was dosed at 0.8 mg/m^2 twice daily with an aim of a plasma therapeutic range between 5-15 ng/ml.

Follow-ups while on sirolimus

Patients were followed up in out-patient clinics one-week and then one-monthly for six-months after commencing and whilst on sirolimus with the followings:

- Clinical assessments; all patients were asked specifically on their symptoms related to vascular malformations, and potential side-effects, and their compliance on taking the sirolimus
- Laboratory blood tests; full blood count, urea and electrolytes, liver function test, serum lipid profile, and plasma sirolimus level
- MRI of the head and neck at the end of the six-months treatment; just before the patient stopped the sirolimus

Each patient was only allowed to continue with the sirolimus therapy upon satisfactory patient tolerance and laboratory investigation results on each follow-up visit during the six-months duration of treatment.

Stopping sirolimus and follow-up

Sirolimus was stopped at the end of the six-months treatment, or if the patients were intolerant to the treatment at any time during the study period. All patients were also followed-up in the out-patient clinic one-month after stopping sirolimus treatment with the followings:

- Clinical history taking and examination including for the symptoms and signs related to the vascular malformations
- QoL questionnaires; SF-36, HADS, and VAS-P.
- Medical photography of the head and neck

Outcome measures

The outcome measures focus on the efficacy consisting of clinical and radiological assessments, and safety of sirolimus at six-months.

Clinical assessments

i) Patient reported symptoms change

ii) QoL assessment with SF-36. The 36 items measure the eight dimensions of physical functioning, role physical, role emotional, energy/fatigue, emotional well-being, social functioning, pain, general health, and health change. Sum scores for mental and physical QoL were computed by first transforming the raw scores into a range with a minimum of 0 and a maximum of 100 with greater scores meaning a better QoL.

iii) HADS - the depression and anxiety subscales comprise seven items each to be rated on a four-point Likert scale (0 = not at all, 3 = mostly; sum score 0-21). A threshold of the depression and anxiety subscales of ≥8 points are defined as clinically relevant.

iv) VAS-P - the score is determined by measuring on the 100 mm line between 'no pain' and the patient's mark, providing a range of scores from 0-100. A higher score indicates greater pain intensity.

Radiological assessment

Vascular malformation lesions were volumetrically segmented on MRI by two independent interventional radiologists (AP and MK). Using Carestream Vue PACS (version 12.0.0.0757 lesion management tool), vascular malformation was segmented manually by tracing each lesion with the mouse. T2-weighted sequences were used and the inconsistence in MRI sequences was due to the variable availability of sequences. For each patient, lesion volume was measured for pre- and six-months treatment (at the end of the six-months treatment but whilst still on sirolimus) and an average was calculated to allow for comparisons.

Safety

The safety of the sirolimus was assessed by patient reported adverse effects related to the medication, and the laboratory blood test results pre-, during and six-months therapy.

Statistical analysis

All statistical analysis was performed using SPSS version 25 statistical software package (SPSS, Armonk, NY: IBM Corporation). Wilcoxon signed-rank test was applied to analyse for differences between pre- and six-months treatment in the scores for SF-36, VAS-P and HADS, and radiological images. P-values <0.05 were considered significant. Repeatability analysis was performed and assessed at two different time points by two radiologists (AP and MK). The interclass correlation coefficient (ICC) was used for this analysis. A two-way mixed-effect model based on single ratings and absolute agreement assess the inter-rater repeatability.

Results

Patient demography and pre-treatment clinical characteristics

A total of seven patients with head and neck low-flow vascular malformations, with a median age of 43 years, and a median follow-up of 19-months were included in the study. Table 1 summarises the patient demography and pre-treatment clinical characteristics of all the patients included in the study.

Patient reported symptom changes related to vascular malformations during and one-month upon stopping sirolimus treatment

Table 2 summarises dose and duration of sirolimus therapy, and the patient reported symptom changes related to vascular malformation during and one-month upon stopping treatment. All six patients who completed the six-months sirolimus therapy reported subjective reduction of swelling with and without other symptom improvement related to the vascular malformations whilst on treatment. However, at one-month review after discontinuation of sirolimus, five patients reported return of initial symptoms, at least partially. Only one patient reported a continued improvement in symptoms upon stopping treatment. One patient who did not complete treatment due to intolerable side-effects, did not report any symptoms change related to vascular malformations.

QoL assessments

Table 3 summarises the SF-36 by domains, HADS and VAS-P scores pre- and six-months sirolimus treatment. The median score amongst all patients in seven out of eight domains, measured by SF-36, were non-significantly higher in six-months treatment when compared to pre-treatment. HADS and VAS-P scores were similar between pre- and six-months treatment. When Wilcoxon signed-rank test was applied, there was no statistically significant differences found between the pre- and six-months treatment scores in all eight domains of SF-36, HADS and VAS-P ($P>0.05$).

Pre- and six-months sirolimus treatment radiological assessment

The ICC for inter-rater reliability was excellent being 1.000 (95% CI 0.978-1.000) and 1.000 (95% CI 0.999-1.000) for pre-treatment and six-months treatment lesion size respectively (Table 4). Figure 2 and Table 5 summarises the vascular malformation lesion size, measured in volume, on MRI pre- and six-months sirolimus treatment. Five patients demonstrated a minimum 10% decrease in lesion size six-months treatment (median 21%, range 13-40%). A Wilcoxon signed-rank test showed that sirolimus treatment did elicit a statistically significant change in lesion size in either direction ($Z = -1.992$, $P = 0.046$).

Safety

Six patients completed the six-months course of sirolimus therapy with one patient (Patient 5) did not complete the treatment due to intolerable side effects; diarrhoea & vomiting, mouth ulcers, facial pain, bleeding and swelling. Symptomatic and laboratory blood test side-effects of all patients were summarized in Table 6. The most common side effects found were dyslipidaemia (n=4) and mouth ulcers (n=2); both required no intervention other than reassurance and monitoring. Dose reduction was required in one patient (Patient 6) due to complaint of ear and throat pain. All symptomatic and laboratory blood test side-effects resolved upon stopping the sirolimus therapy. All other laboratory blood tests (FBC, urea and electrolytes, and liver function) did not demonstrate any significant alteration from sirolimus treatment. Statistical analysis of comparison of pre- and post-treatment laboratory results demonstrated no statistical significance (results not shown).

Discussion

Historically, symptomatic vascular malformations have been primarily treated by procedural interventions such as excision and debulking, if conservative or supportive therapy is inadequate. More recently, endovascular therapy has become the main interventional therapeutic tool in the management of vascular malformations. Increased understanding of the pathogenesis of vascular malformations has enabled a role for medical therapy as specific inhibitors may be potentially used. In particular medical treatment is useful in treating complex vascular malformations that are diffuse or not amendable to surgery or endovascular treatment.

Sclerotherapy and surgical interventions for low-flow vascular malformations carry potential risks including bleeding, end-organ ischaemia, tissue ulceration, and nerve injury. In addition, intervening on the head and neck vascular malformation may pose further challenges related to its complex anatomy which includes the presence of many vital structures such as the airway, brain, major nerves including the cranial nerves, pharynx, ear and eyes, as well as the cosmetic implications. For example, this is evident in treatment where special precautions need to be taken, for example when performing sclerotherapy near the parotid gland, as damage to the facial nerve can occur causing facial paralaysis.[16] Prophylactic tracheostomy may be required in cases where airway may be compromised post-operatively.

The total number patients allowed to be recruited in this case series was limited by the strict protocol of our local drug and therapeutic committee who would review the outcomes before deciding on if the sirolimus treatment could be offered to more patients including those with vascular malformations of other anatomical sites.

Therefore, the suitability of these seven cases, which represented approximately 20% of all our head & neck low-flow vascular malformations managed in the clinic during the study period, was reviewed on a case-to-case basis by the multi-disciplinary team. These cases were among the most challenging in terms of their suitability for interventional or surgical therapy and/or refractory to standard treatment, hence were trialled for sirolimus treatment provided that they meet all the inclusion criteria of the study. All the patients were symptomatic, and counselled thoroughly with the risks and benefits of the trial of sirolimus treatment. There was no rescue treatment during the treatment of sirolimus.

In this case series, most patients demonstrated beneficial response with a partial reduction in lesion size on MRI scan six-months treatment (Figure 1). Side-effects experienced by patients were mainly hypercholesterolaemia, hypertriglyceridemia and mouth ulcers (Table 6). Despite many side-effects reported, these were generally mild and tolerable. Upon consultation, an agreed decision, with patient participation, was made whether to continue on treatment after weighing up risks and benefits. However, the final decision was with the patient whether to continue or withdraw from the study. Commonly reported side-effects of sirolimus in the literature include mucositis, headaches, lethargy, gastrointestinal side effects, peripheral oedema, hypertension and impaired healing.[17] Sirolimus has been also been reported to have haematological (thrombocytopenia, leukopenia, anaemia, microcytosis) and metabolic effects (hyperlipidaemia, hyperglycaemia, increased levels of liver enzymes).[17-21] In our cohort of patients, all haematological, renal and liver laboratory investigations were within normal limits. The most significant metabolic adverse reactions associated with sirolimus are hyperlipidaemia and hypertriglyceridaemia.[22,23] In our cohort of patients,

the adverse metabolic effects required no intervention and this could be as a result of the younger age within our patient sample. However, it should be noted that long-term use of sirolimus can result in cases of severe dyslipidaemia and may require management with lipid-lowering agents.[24,25] Upon follow-up one-month post-treatment, five patients reported return of symptoms upon discontinuation of treatment and one patient reported continued improvement in symptoms.

Sirolimus has been in use since 2010 for the management of vascular malformations. A recent systematic review assessing the efficacy and safety of sirolimus in the treatment of vascular anomalies concluded that sirolimus can improve the prognosis of vascular anomalies, most notably vascular tumours associated with life-threatening coagulopathy and venous and lymphatic malformations.[15] In 2016, Adams *et al*[13] conducted a study on 61 patients with complex vascular anomalies and demonstrated over 80% partial response with sirolimus. More recently, Hammer *et al*[26] published results of a phase II trial of sirolimus in the treatment for extensive and/or complex slow-flow vascular malformations. This study showed 16 patients had significant improvement of their symptoms and QoL. Vascular anomalies is an umbrella term that encompasses vascular tumours and vascular malformations, where the former arises by cellular hyperplasia and are characterized by increased proliferation rates of endothelial and other vascular cells such as pericytes. These lesions are not clinically present at birth, demonstrate rapid growth, and spontaneous resolution over a period of time.[28] In comparison, vascular malformations are characterized as an error in the development of vascular embryonic tissue. These lesions usually present at birth, show a lack of endothelial cell proliferation, and show progressive growth in proportion to the child and do not involve spontaneously over a period of time.[29] The exact mechanism in how

mTOR inhibitors is beneficial in vascular malformations is poorly understood. However, it is likely that its antiproliferative/antiangiogenic activity is effective in abnormal growth that are associated with vascular malformations.

Limitations

The limitations of our study include a small patient sample size, the lack of a control group (i.e. no placebo cohort of patients), which will affect statistical analysis in aspects such as pre- and six-months treatment quality of life, and the relatively short duration of follow-up in the study. Despite this, inclusion of statistical analysis is still a more robust method of reporting the findings than just descriptive statistics especially these data could be used in the planning and design of future longitudinal clinical trials with adequate power calculation for sample size and feasibility. The study also did not demonstrate the evidence of the optimal duration of the sirolimus treatment. Furthermore, there might be biases due to the non-randomised nature of the study, and assessors and patients were not blinded. Nevertheless, our study showed that sirolimus may be considered as a treatment option in patients with low-flow vascular malformations where invasive treatments are contra-indicated or pose high risk of complications.

Further larger research, particularly multi-centre randomised trial with control groups is required to monitor long-term outcomes, determining optimal dose and duration of treatment. In addition, genetic testing can help identify patients with mutations who may benefit from a mTOR inhibitor such as sirolimus. Investigating other pharmacological agents (e.g. copanlisib, ponatinib) that are known to inhibit the

pathways involved in the pathogenesis of vascular malformations will help provide alternative treatment options in the future.

Conclusion

In our preliminary experience, sirolimus seemed effective and safe in treating patients with complex head and neck low-flow vascular malformations. This provides an alternative less invasive therapeutic option where interventional treatment is challenging and/or refractory. These are initial observations only, and further research is required to confirm, quantify and characterise these findings.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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Table 1

Patient	Age/Gender	Type and location of the vascular malformation	Symptoms/signs at diagnosis	Previous intervention
1	49/Female	Left cheek predominantly venous malformation	Swelling Aesthetics concerns	Sclerotherapy
2	24/Male	Left lip and face predominantly venous malformation	Swelling Aesthetics concerns	Sclerotherapy, debulking surgery, and Laser therapy
3	26/Female	Oral cavity predominantly lymphatic malformation	Swelling Aesthetic concerns Speech difficulties Discomfort	Sclerotherapy and surgical excision
4	60/Female	Peri-pharyngeal predominantly venous malformation	Swelling Difficulty with lateral movement of head Recurrence sense of need to swallow Sense of restriction Unable to bend over	Sclerotherapy

			Sleeps upright Temporary voice loss	
5	43/Male	Left lower face predominantly venous malformation	Swelling Aesthetic concerns Slurred speech	None
6	48/Female	Peri-pharyngeal predominantly venous malformation	Headache Ear ache Dysphagia Reduced voice	None
7	23/Male	Base of tongue extending to bilateral submandibular regions predominantly lymphatic malformation	Fullness and discomfort on the face	Sclerotherapy

Table 2

Patient	Sirolimus dose	Duration of treatment	Symptom changes related to vascular malformations during treatment	Symptom changes related to vascular malformations one-month upon stopping treatment
1	1.5 mg twice a day	6 months	Left cheek slight reduction in swelling	Recurrence of symptoms Increased fullness of face
2	2.0 mg twice a day	6 months	Slight reduction in swelling	Return of swelling
3	1.0 mg twice a day	6 months	Reduced tongue swelling, more energetic, Reduced pain	Return of swelling Recurrence of pain Difficulty speaking
4	1.5 mg twice a day	6 months	Reduced fullness around pharynx, able to bend over for short period of time, able to lie flat at night	Return of temporary voice loss and unable to lie flat

5	2.0 mg twice a day	3 weeks	No change	No change
6	1.5 mg twice a day Reduced to 1.0 mg twice a day after one month	6 months	Reduced pain, Less pronounced migraines	Return of ear ache and migraines
7	1.5 mg twice a day	6 months	Reduced swelling of face	Symptoms continue to improve

Table 3

	Median (interquartile range)		
	Pre-treatment	**Six-months treatment**	**P value**
SF-36 domains			
General health	42 (44)	50 (26)	0.498
Physical functioning	90 (30)	62.5 (39)	0.223
Role functioning/physical	50 (100)	62.5 (62.5)	0.285
Role functioning/emotional	33 (83)	83 (58)	0.285
Energy/fatigue	20 (47.5)	55 (29)	0.176
Emotional well-being	20 (70)	68 (38)	0.138
Social functioning	50 (12.5)	69 (41)	0.395
Pain	78 (66)	82.5 (27)	0.339
HADS			
Anxiety	5 (6.5)	5 (6)	0.593
Depression	4 (6.5)	5 (6.5)	0.750
Pain			
VAS-P	2 (48.5)	7 (36.5)	0.223

Table 4

	Lesion size in volume pre-treatment		Lesion size in volume six-months treatment		Intraclass correlation coefficient in pre-treatment lesion size	Intraclass correlation coefficient in six-months treatment lesion size
	AP	MK	AP	MK		
Patient 1	17.2cm^3	17.6cm^3	14.0cm^3	13.5cm^3	1.000	1.000
Patient 2	72.8cm^3	74.0cm^3	64.2cm^3	63.8cm^3		
Patient 3	38.5cm^3	39.3cm^3	32.3cm^3	32.9cm^3		
Patient 4	36.2cm^3	36.6cm^3	39.0cm^3	38.6cm^3		
Patient 5	Did not assess*		Did not assess*			
Patient 6	17.6cm^3	18.2cm^3	12.5cm^3	12.9cm^3		
Patient 7	145.0cm^3	146.0cm^3	87.8cm^3	88.2cm^3		

*Patient 5 MRI was not assessed as patient withdraw from study after three-weeks

Table 5

	Average lesion size in volume pre-treatment	Average lesion size in volume six-months treatment	Volume size difference between pre- and six-months treatment
Patient 1	17.4cm^3	13.75cm^3	Reduced by 21%
Patient 2	73.4cm^3	64cm^3	Reduced by 13%
Patient 3	38.9 cm^3	32.6cm^3	Reduced by 16%
Patient 4	36.4cm^3	38.8cm^3	Increased by 7%
Patient 5	Did not assess*	Did not assess*	Not applicable
Patient 6	17.9cm^3	12.7cm^3	Reduced by 29%
Patient 7	145.5cm^3	88cm^3	Reduced by 40%

*Patient 5 MRI was not assessed as patient withdraw from study after three-weeks

Table 6

Patient	Symptomatic side effects	Laboratory blood test side effects
1	Minor abdominal discomfort, lethargy	None
2	Flu-like symptoms, lethargy, increased bowel movements	Mild hypertriglyceridemia
3	None	Mild hypercholesterolemia
4	Mouth ulcers, scalp pustules, urinary incontinence, chest infection	Mild hypercholesterolemia
5	Diarrhoea and vomiting, mouth ulcers, facial pain, bleeding, swelling	Mild hypertriglyceridemia
6	Ear and throat pain on initial dose but no side effects upon reduced dose	None
7	None	None

Figure 1. Treatment pathway of low-flow head & neck vascular malformations using Sirolimus

Figure 2. T2-weighted images demonstrating pre-treatment MRI scan (A1-E1) and six-months treatment MRI scan (six-months later) (A2-E2). With sirolimus, the lesion volume decreased in these five patients.

Table 1: Patient demography and pre-treatment clinical characteristics of all the patients receiving sirolimus treatment for head and neck vascular malformations

Table 2: Dose and duration of sirolimus therapy, and the patient reported symptom changes related to vascular malformations change during and one-month upon stopping treatment

Table 3: Pre- and six-months sirolimus treatment quality of life, anxiety, depression and pain scores

Table 4: Inter-rater variability between pre- and six-months sirolimus treatment on vascular malformation lesion size

Table 5: Pre- and six-months sirolimus treatment vascular malformation lesion size, measured in area, on magnetic resonance imaging

Table 6: Patient reported side-effects during the treatment period