Everolimus

- **Treatment of medically refractory epilepsy associated with tuberous sclerosis complex**
- **Status on the first Danish pediatric patients**

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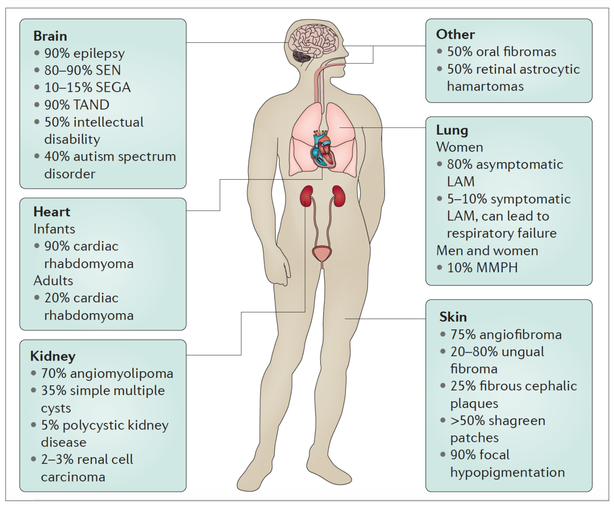
Background:

Tuberous sclerosis complex (TSC) is an autosomal dominant disease which in Denmark has an incidence of 5-10/year and a prevalence of approximately 200-400 cases. It is a multi-organ disease (Fig. 1). Epilepsy is frequent, and two-thirds of patients are refractory to anti-epileptic medication.



Henske et al 2016[1]

Fig. 1

Dysfunction of the tumor suppressing hamartin/tuberin complex leads to an overactivated mTOR signaling pathway and uncontrolled cell growth (Fig. 2a). Everolimus is an inhibitor of the mTOR pathway and reduces cell proliferation (Fig 2b). Protocolled treatment of TSC associated epilepsy with everolimus has recently been approved by The Danish Medicines Council. The progress in the treatment of the first pediatric patients is described here.

Materials & Methods:

Four pediatric patients at Rigshospitalet have met the criteria from The Danish Medicines Council (Table 1) for everolimus therapy since August 2017. Evaluation of treatment effect and decision of continued treatment is done after 4 and 12 months of adequate p-everolimus levels (Table 1).

References
1. Henske *et al. Nat. Rev. Dis. Primers,* 2016 May; Vol 2, 16035. 2. Northrup *et al. Pediatr Neurol.* 2013 Oct; 49(4): 243–254 3. Krueger *et al. Eur. J. Paediatr. Neurol.* 2018 Jul 4; Epub ahead of print. 4. Davies *et al. Orphanet J Rare Dis.* 2017 Feb; 12:35

Results

Three patients reached adequate p-everolimus levels in 44-72 days (median 57 days). Levels below target were frequent due to drug interactions and/or pausing of everolimus because of neutropenia (Fig. 3). Reduction in seizures after 4 months was >50% for two patients. The remaining two patients have not yet passed four months of therapeutic levels (Table 2). One of the three patients became seizure free after concomitant epilepsy surgery.

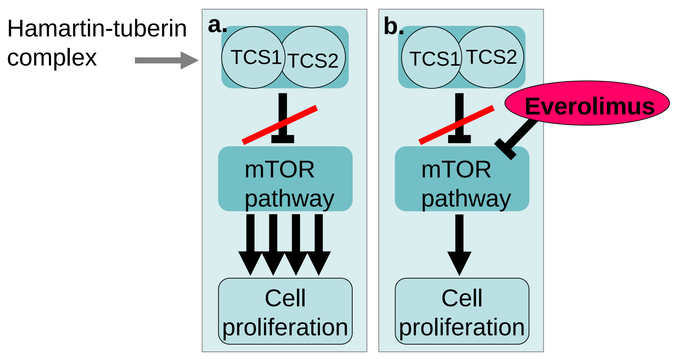


Fig. 2

Timeline

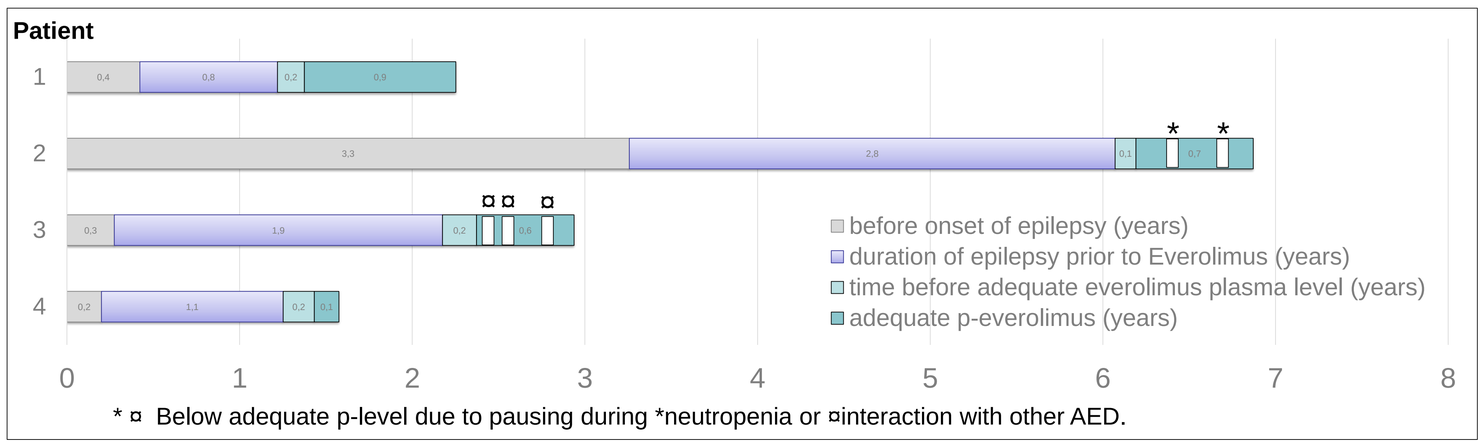


Fig. 3

Conclusions:

Early data on everolimus as adjunctive treatment in TSC associated epilepsy is promising with regards to both effect and tolerability. Close monitoring is warranted[4].

Starting criteria
• TSC diagnosis (clinical or genetic criteria)[2]
• Medically refractory epilepsy
• NVS/ ketogenic diet considered
• Frequent seizures with great impact on daily life (> weekly seizures)
• No contradictions to everolimus
• Expected good compliance

Stop criteria
• Seizure reduction < 33% after 4 months of adequate p-everolimus levels
• Seizure reduction < 50% after 12 months of adequate p-everolimus levels
• Intolerable side effects

Table 1

Patient characteristics and effects of everolimus treatment

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	F	F	M	M
Current age	2y 3m	6y 10m	2y 11m	1y 7m
Genetic aetiology	TSC2 variant	No TSC1/2 variant found	TSC2 variant	TSC2 variant
Ketogenic diet	Yes, previously	No, not possible	Yes, previously	Yes, currently
VNS	No	Yes, currently	No	No
Epileptic surgery	Yes	No	Yes	No
SEGA	No	No	No	Yes, small
Other TSC manifestation	Renal angiomyolipoma	Renal cysts	Cardiac rhabdomyoma Renal angiomyolipoma	Cardiac rhabdomyoma Hypertension, renal cysts
AED hist.	OXC,TPM,LEV, ZNS	VPA,TPM,LTG,CBZ,LEV, ZNS,VGB,SUL,CLB	LEV,CLB	CBZ,hydrocortisone
AED current	VPA,VGB,CLB	ESL, RUF	TPM, VGB, CBZ	OXC, VGB, LEV
Weekly seizures prior to everolimus	140 brief complex partial seizures	30 complex partial seizures weekly + >50 absences daily	20 complex partial seizures	160 complex partial seizures
Weekly seizures after 4 months of adequate p-everolimus	58	- (After 3 months: 15 seizures/w + 16 new shorter seizures/w + 20-40 absences daily)	0	- (after 1 month:0)
Other effects	Positive psychomotor development	Positive psychomotor development	Positive psychomotor development	Positive psychomotor development
Side effects	Mild, self limiting exanthema	None, possibly diarrhea	Neutropenia during minor infections,	None

Table 2