Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Stick or twist: Everolimus for seizures in tuberous sclerosis complex during the COVID-19 pandemic

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Dear Editors,

As the coronavirus disease 2019 (COVID-19) pandemic continues globally, protecting the health of vulnerable people with epilepsy (PWE) remains a priority. Many people with tuberous sclerosis complex (TSC) reside in long-term care facilities (LTCFs), which are high risk settings for infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and severe COVID-19 [1]. Pre-existing respiratory disease is associated with an increased risk of severe COVID-19, which may be relevant to those with lymphangioleiomyomatosis (LAM), a progressive cystic lung disease infrequently seen in women with TSC [2].

The EXIST-3 trial demonstrated that everolimus, a mechanistic target of rapamycin (mTOR) inhibitor, was effective at reducing seizures in TSC [3]. Neurologists may be reluctant to use mTOR inhibitors during the pandemic due to their apparent immunosuppressive activity. However, mTOR inhibitors prevent organ rejection by an immunostimulatory mechanism, via selective expansion of regulatory CD4+ T cells. Indeed, transplant recipients on mTOR inhibitors are less likely to develop cytomegalovirus infection than those treated with other immunosuppressive agents [4].

We initiated everolimus for TSC-related seizures in five adults between September and December 2020. All had highly active epilepsy (73 seizures per month, mean) and had trialled a mean of eight anti-seizure medications. A 31-year-old male resident in a LTCF started everolimus for frequent injurious atonic and tonic seizures in November 2020. Two months later, he developed pyrexia of 38.6 °C, without respiratory

Table 1
Clinical characteristics and outcomes of people with TSC-related epilepsy on mTOR inhibitors who developed COVID-19.

Patient	Age (yrs)	TSC mutation	Clinical features	mTORi	COVID-19 symptoms	SARS-CoV-2 RT-PCR	Hospital admission	Outcome	mTORi stopped	Reference
I	31	TSC2	DRE, ID, AML	EV 10mg	Fever	Positive	No	Full recovery	No	Current
II	16	TSC2	DRE, ID, SEGA, AML, RM	EV 3mg	Fever, cough, arthralgia	Not tested[a]	No	Full recovery	No	Peron et al, 2020
III	8	TSC2	DRE, ID, SEGA, RM	EV 3mg	Fever, diarrhea, pneumonia	Not tested[a]	Yes	Full recovery	No	Peron et al, 2020
IV	25	TSC2	DRE, ID, SEGA, RM, AML	EV 5mg	Fever, cough	Not tested$_1$	No	Full recovery	No	Peron et al, 2020
V	6	TSC2	DRE, ID, RM, AML	EV 4mg	Fever, pneumonia	Not tested[a]	No	Full recovery	Yes	Peron et al, 2020
VI	41	Not stated	LAM	EV 10mg	Fever, dyspnea	Positive	No	Full recovery	No	Baldi et al., 2020
VII	51	Not stated	LAM	SIR (dose not stated)	Fever, cough	Positive	Yes	Full recovery	No	Baldi et al., 2020

[a] Limited availability of SARS-CoV-2 PCR testing during study period. Patients either met criteria of suspect case or presented with at least two symptoms of COVID-19 or were a close contact of a confirmed case.

Abbreviations: AML, angiomyolipoma; COVID-19, coronavirus disease 2019; DRE, drug-resistant epilepsy; EV, everolimus; ID, intellectual disability; LAM, lymphangioleiomyomatosis; mTORi, mechanisitic target of rapamycin inhibitor; RM, rhabdomyoma; SEGA, subependymal giant cell astrocytoma; SIR, sirolimus; TSC, tuberous sclerosis complex.

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symptoms or requirement for hospitalisation. Nasopharyngeal real-time PCR confirmed SARS-CoV-2 infection. His seizure frequency remained stable throughout the viral illness. His serum everolimus level measured two weeks after recovery was 5.8 ng/ml (5–15 ng/ml).

In a literature review, we identified 6 additional cases of COVID-19 in people with TSC on mTOR inhibitors (Table 1) [5, 6]. All made a full recovery. Two were admitted to hospital with COVID-19 pneumonia. Everolimus was temporarily discontinued in one patient. Data from kidney and liver transplant centres did not identify an increased risk of severe COVID-19 in transplant recipients on mTOR inhibitors [7, 8].

RNA viruses, such as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) modulate the mTOR pathway during infection. Everolimus decreased MERS-CoV replication *in vitro* [9]. Low-dose everolimus therapy reduced the annual rate of respiratory infections and enhanced the response to influenza vaccination in elderly volunteers [10]. A number of clinical trials are underway to study the efficacy and safety of mTOR inhibitors for COVID-19 [11]. The immunorestorative effects of rapamycin may enhance the efficacy of COVID-19 vaccines. We have encouraged vaccination in our TSC patients and advised continued treatment with everolimus, despite the lack of specific data regarding COVID-19 vaccination in patients receiving mTOR inhibitors. In our centre, seven TSC patients on mTOR inhibitors were vaccinated without complication.

The TSC Alliance advised cautious use of mTOR inhibitors during the pandemic and to consider temporary discontinuation in those exposed to the virus or in cases of active COVID-19 [12]. However, some of this trepidation may be overstated and we conclude that there is rationale to initiate and continue mTOR inhibitors for TSC-related epilepsy during the pandemic.

Declarations of Competing Interest

None

Consent to participate

The patient reported in this letter lacked decision-making capacity. We obtained consent from his legal guardian to allow for reporting of his data.

Consent for publication

The patient reported in this letter lacked decision-making capacity. We obtained consent from his legal guardian for publication of his data.

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