RAPID COMMUNICATION

Tuberous sclerosis complex (TSC), lymphangioleiomyomatosis, and COVID-19: The experience of a TSC clinic in Italy

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Abstract
Individuals with comorbidities are at higher risk of coronavirus disease 2019 (COVID-19) and worse outcome, but little information has been available about patients with genetic diseases and COVID-19. This study aims at evaluating the presence and outcome of COVID-19 in a cohort of Italian patients with tuberous sclerosis complex (TSC) and/or lymphangioleiomyomatosis (LAM), and at reviewing the possible effects of mTOR inhibitors on SARS-CoV-2 infection. We included 102 unselected individuals with a diagnosis of TSC and/or LAM assessed between January 1, 2020 and April 24, 2020 (29% children, 71% adults). Twenty-six patients were on mTOR inhibitors. Demographic data, TSC manifestations, presence, and outcomes in individuals with confirmed or suspected SARS-CoV-2 infection were evaluated. Health status and outcomes of all patients on mTOR inhibitors were assessed. One patient with severe TSC had polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection, was admitted to ICU, and died. Nine additional patients either met the definition of suspect case or presented with at least two of the most common symptoms of SARS-CoV-2 infection. All recovered fully. None of the patients treated with mTOR inhibitors for their underlying comorbidities was diagnosed with COVID-19, and those who showed suspicious respiratory symptoms recovered fully. This cohort study provides preliminary information on COVID-19 in people with TSC in Italy and suggests feasibility to systematically evaluate the role of mTOR inhibitors in SARS-CoV-2 infection.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has so far affected over 5 million people worldwide, and the Lombardy region in Italy was one of the first and most impacted areas after Wuhan, China (Zehender et al., 2020). Individuals with comorbidities are at higher risk of infection and worse outcome (Wu et al., 2020), but little information has been available about patients with rare genetic diseases and COVID-19.

Tuberous sclerosis complex (TSC) is one of the most common rare diseases, affecting 1 in 6,000 live births and causing multisystem morbidities in the brain, kidneys, heart, eyes, and skin (Northrup & Krueger, 2013). Adult women may have cystic pulmonary involvement (lymphangioleiomyomatosis [LAM]) that could lead to respiratory insufficiency (Northrup & Krueger, 2013). A sporadic form is also described in previously healthy women (S-LAM; Northrup & Krueger, 2013). The only approved treatment is the use of mTOR inhibitors (Everolimus...
and Sirolimus), originally identified as immunosuppressants (Franz & Krueger, 2018).

Recommendations for patients with TSC during the COVID-19 pandemic are currently based on expert opinions (Tuberous Sclerosis Alliance, 2020; https://www.tsalliance.org/wp-content/uploads/2020/03/COVID-19-Considerations-for-TSC-Medical-Professionals-WEB.pdf). To provide evidence for these recommendations, we performed a study to investigate the presence and outcomes of SARS-CoV-2 infection in a cohort of Italian TSC patients.

2 | METHODS

This retrospective cohort study was conducted at the multidisciplinary TSC Clinic of San Paolo University Hospital in Milan and was approved by the Institution’s Ethics Committee. The institution is currently operating as a COVID hospital, with an ICU and six COVID wards, and the remaining COVID-free wards ensuring essential services. Our TSC clinic is the largest in Italy, comprises a dedicated LAM clinic, and offers diagnosis and care to 388 affected children and adults from various parts of the country (Peron et al., 2018).

We included in the study all individuals affected with TSC and/or LAM who were seen in the outpatient clinics between January 1, 2020 and April 24, 2020 (corresponding to the surge of the epidemiological curve in Italy) during regular visits before the lockdown and for essential in-person clinical encounters thereafter. We included also the patients assessed through phone visits after the lockdown. Although the first confirmed community spread of COVID-19 in Italy was identified on February 21, we decided to extend the assessment period back to January as there is evidence that SARS-CoV-2 was present in the country since then (Zehender et al., 2020).

We reviewed all medical records to identify confirmed SARS-CoV-2 infections and/or suspect cases as defined by the European Center for Disease Prevention and Control (2020) or the World Health Organization (https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov). Changes in clinical status strictly related to TSC are not reported for the purpose of this article.

To investigate a possible effect of mTOR inhibitors, patients with LAM on Sirolimus and TSC patients on Everolimus were interviewed on April 17, 2020 and April 24, 2020, respectively. Patients and/or caregivers were asked to respond referring to the last 4 months.

Data collected included demographics, TSC manifestations, SARS-CoV-2 testing, history of signs/symptoms suggestive of COVID-19, hospital admissions, treatments, and outcomes. Patients were instructed to notify the TSC clinic of later changes in health status.

3 | RESULTS

A total of 102 individuals with TSC and/or LAM were included. Demographic characteristics are summarized in Table 1 and treatment with mTOR inhibitors in Table 2. Prevalence of TSC-related manifestations and molecular diagnosis were in line with those of the literature (Northrup & Krueger, 2013), and phenotypes were of variable severity (Peron et al., 2018), ensuring this is a representative sample of the general TSC population.

| Table 1 | Demographic characteristics of the cohort |
| --- | --- |
| Total number of patients | 102 |
| Rare disease diagnosis |  |
| Definite diagnosis of TSC | 93/102 (91%) |
| Sporadic LAM | 9/102 (9%) |
| Pre-existing pulmonary involvement (calculated on adults) |  |
| TSC–LAM | 13/72 (18%) |
| Sporadic LAM | 9/72 (13%) |
| Total | 22/72 (31%) |
| Sex |  |
| Females | 64/102 (63%) |
| Males | 38/102 (37%) |
| Age |  |
| Whole cohort | 102 |
| Median age | 25 years |
| Age range | 2 m–72 years |
| Children | 30/102 (29%) |
| Median age | 8 years |
| Age range | 2 m–17 years |
| Adults | 72/102 (71%) |
| Median age | 36 years |
| Age range | 18–72 years |
| Current residence |  |
| Northern Italy | 83/102 (81%) |
| Lombardy | 71 |
| First endemic areas | 14 |
| Central/southern Italy | 15/102 (15%) |
| Outside Italy | 4/102 (4%) |
| Patients living in their homes | 97/102 (95%) |
| Patients living in assisted living facilities | 5/102 (5%) |
| SARS-CoV-2 testing |  |
| Performed | 6/102 (6%) |
| Not performed | 77/102 (75%) |
| Information not available | 19/102 (19%) |
| Testing performed in the Italian population (as of April 24, 2020) | 1,642,356/60,474,050 (3%) |

Abbreviations: LAM, lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.

aThe first endemic areas in northern Italy are identified as Codogno, Bergamo, and the Padua province.
bItalian patients who were living abroad at the time of the interview or were out of the country during the pandemic and could not go back to Italy.
cAssumed not to be tested, as only symptomatic individuals presenting to the emergency department or requiring hospitalization received nasopharyngeal swab in Italy as per government recommendations.
suggestive of SARS-CoV-2 infection. Two of them which are known risk factors and might have influenced the severity of disease, and was not on Everolimus.

Infections occurred. In such case, patients were advised to contact the TSC/LAM clinics, and adjustments in dosage or interruption of treatment out of 71 living in Lombardy in our sample (0.014, 95% CI [<0.0001–0.0829]) would be in line with these numbers.

Since it is impossible to differentiate COVID-19 from community acquired respiratory infections based solely on signs and symptoms, we identified nine patients who reported symptoms suggestive of COVID-19, without confirmative reverse transcriptase polymerase chain reaction (RT-PCR) testing. One of these patients tested negative for SARS-CoV-2 on RT-PCR from nasopharyngeal swab. Despite being the gold standard for the diagnosis, RT-PCR has high rates of false negative results (Younes et al., 2020), and the Food and Drug Administration (2020) concluded that negative results do not preclude SARS-CoV-2 infection (https://www.fda.gov/media/134922/download). Therefore, we cannot rule out COVID-19 in this patient. Conversely, it is also possible that some of the suspect cases listed in Table 3 exhibited symptoms due to different causes, since testing was not performed in them. No data are available about suspected cases in the general population for comparison, and only future serological testing of IgG antibodies will be able to determine whether TSC patients are more susceptible (or less susceptible) to symptoms.

Our results suggest that TSC patients do not have an increased risk of developing COVID-19. Alternatively, these numbers could be explained by the excellent compliance to social distancing demonstrated by our patients and their families during this pandemic. On the other hand, the only patient with confirmed COVID-19 had unfavorable outcome. It must be noted that he was a male older than 60 years, who had severe TSC with several comorbidities and was living in an assisted living facility with the potential for high inoculum, which are known risk factors and might have influenced the severity of disease, and was not on Everolimus.

We kept contact with all the patients on mTOR inhibitors and advised not to discontinue existing treatment, unless respiratory infections occurred. In such case, patients were advised to contact the TSC/LAM clinics, and adjustments in dosage or interruption of treatment were evaluated on a case-by-case basis after considering risks and benefits. None of the patients on Sirolimus or Everolimus had a possible that some of the suspect cases listed in Table 3 exhibited symptoms.

All patients/caregivers reported they were strictly abiding to national recommendations, namely lockdown. Those allowed to go for a walk because of underlying comorbidities such as intellectual disability and autism spectrum disorder were practicing social distancing when outside their homes. Twenty-four of 26 patients who were on mTOR inhibitors continued treatment (those who discontinued treatment are displayed in Table 3).

Complete information was available for all 102 patients until the end of February, and for 99/102 patients until the end of collection. As of April 24, one TSC patient had polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection. Nine additional patients either met the definition of suspect case (https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov) (5), or presented with at least two of the most common symptoms of SARS-CoV-2 infection (World Health Organization, 2020: www.who.int/health-topics/coronavirus#tab=tab_3) (3), or were a close contact of a confirmed case (https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov) (1). Two of them required admission to the hospital, and seven were treated at home. Detailed phenotype, therapy with mTOR inhibitors, clinical course, and outcome are reported in Table 3. Nine additional patients described mild isolated respiratory symptoms that were judged non-suggestive of SARS-CoV-2 infection.

4 | DISCUSSION

To our knowledge, this is the first study of a rare genetic disease in a SARS-CoV-2-affected area. Although expert recommendations concerning COVID-19 and rare diseases are published (Orphanet, 2020; http://international.orphanews.org/summary/editorial/nl/id-200327.html) and funding has been appropriated for studies expanding focus on this subject (National Institutes of Health, 2020), the prevalence and outcomes of COVID-19 in a rare disease cohort has not been reported.

At time of writing, the Lombardy region had a cumulative incidence of 739 confirmed cases of SARS-CoV-2 per 100,000 inhabitants (0.007) (Istituto Superiore di Sanità, 2020; https://www.epicentro.iss.it/ coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_28-aprile-2020.pdf). As a comparison, the identification of only one TSC patient with confirmed SARS-CoV-2 infection out of 71 living in Lombardy in our sample (0.014, 95% CI [<0.0014–0.0829]) would be in line with these numbers.

Abbreviations: LAM, lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.
### Characteristics of the TSC and LAM patients with confirmed SARS-CoV-2 infection, who met the definition of suspect cases, presented with at least two of the most common symptoms of SARS-CoV-2 infection, or were close contacts

| Sex | Age | Ethnicity | Residence* | TSC manifestations | TSC mutational status | mTOR inhibitors | Timeline of symptoms | Hospital admission | Testing for SARS-CoV-2 | ICU | Outcome |
|-----|-----|-----------|-------------|-------------------|----------------------|-------------------|---------------------|--------------------|----------------------|------|---------|
| M   | 61  | Caucasian | Northern Italy—in a group setting (assisted living facility in Lombardy) | Severe ID, ASD, drug-resistant seizures, cortical tubers, subependymal nodules, retinal hamartomas, hypomelanotic macules, facial angiofibromas, fibrous cephalic plaque, shagreen patch, ungual fibromas, cardiac rhabdomyomas | TSC2 | No | April 14, 2020: admitted to a COVID ward with fever and \(O_2\) desaturation, bilateral interstitial pneumonia. Placed on helmet-based ventilation, unable to eat, fed and given antiepileptic drugs through NG tube. April 17, 2020: clinically stable, was able to eat. April 19, 2020: sudden worsening of symptoms, onset of renal failure. Moved to ICU, intubated and sedated. CRP: 327 mg/L; D-dimer: 2,921 ng/mL (nv < 500); creatinine: 2.33 mg/dL; azotemia: 121 mg/dL. Worsening bilateral interstitial pneumonia | Yes | Positive | Yes | Deceased |
| F   | 16  | Caucasian | Northern Italy—at home (Lombardy) | Severe ID, ADD, ASD, drug-resistant seizures, cortical tubers, subependymal nodules, SEGA, hypomelanotic macules, facial angiofibromas, cardiac rhabdomyomas, renal angiomyolipomas | TSC2 | Everolimus (3 mg/day) | March 12, 2020: onset of fever, bronchitis, dry cough for a week, followed by asthenia. Treated with cephalosporin | No | No | No | Full recovery |
| F   | 8   | Caucasian | Northern Italy—at home (endemic area in Lombardy) | Moderate ID, drug-resistant seizures, cortical tubers, subependymal nodules, SEGA, retinal hamartoma, hypomelanotic macules, facial angiofibromas, fibrous plaque, cardiac rhabdomyomas with infantile arrhythmia | TSC2 | Everolimus (3 mg/day) | January 21, 2020: onset of fever (40°), rhinitis, followed by bilateral conjunctivitis on Day 1, diarrhea on Day 3, and anorexia and asthenia. January 25–31, 2020: admitted and diagnosed with left pneumonia. Normal white blood cell count: CRP 12.1 mg/dL. Negative for pneumococcal infection. Treated with paracetamol, cephalosporin, ampicillin/sulbactam | Yes | No | No | Full recovery |
| M   | 22  | Caucasian | Northern Italy—at home (Emilia Romagna) | Severe ID, ADHD, behavioral issues, drug-resistant seizures, hypomelanotic macules, facial angiofibromas, fibrous cephalic plaque, shagreen patch, ungual fibromas, cardiac rhabdomyomas with arrhythmia, renal and hepatic angiomyolipomas, renal cysts | Pending | No | March 10, 2020: onset of fever, anorexia, and asthenia (a few days later, the patient's father was admitted with bilateral interstitial pneumonia and RT-PCR confirmed SARS-CoV-2 infection) | No | No | No | Full recovery |

*Denotes residence associated with SARS-CoV-2 transmission.
| Sex | Age | Ethnicity | Residence* | TSC manifestations | TSC mutational status | mTOR inhibitors | Timeline of symptoms | Hospital admission | Testing for SARS-CoV-2 | ICU | Outcome |
|-----|-----|----------|------------|-------------------|----------------------|------------------|------------------|-------------------|----------------------|------|---------|
| F   | 31  | Caucasian | Northern Italy—at home (Lombardy) | Mild ID, personality disorder, seizures, cortical tubers, subependymal nodules, SEGA, white matter radial migration lines, retinal hamartomas, hypomelanotic macules, facial angiofibromas, fibrous plaques, ungual fibromas, MMPI, renal angiomyolipomas (bilateral nephrectomy) | TSC2 | No | April 24–30, 2020: admitted with fever and cough. Normal white blood count; CRP: 5.7 mg/L; pro-calcitonin: 0.74 mg/mL (nv < 0.15). Chest X-ray: diffuse bilateral interstitial markings | Yes | Negative | No | Full recovery |
| F   | 50  | Asian     | Northern Italy - at home (endemic area in Lombardy) | Sporadic LAM, with impaired lung function | - | Sirolimus (1 mg/day) | March 2020: fever for 20 days and O2 desaturation (to 80%). Treated with supplemental oxygen (already available to the patient because of LAM), paracetamol, amoxicillin (10 days), and levofloxacin (10 days). Refused admission to the hospital. Sirolimus was discontinued, and resumed 10 days after fever resolved | No | No | No | Full recovery |
| M   | 25  | Caucasian | Northern Italy—at home (Lombardy) | Mild ID, seizures, cortical tubers, subependymal nodules, SEGA, hypomelanotic macules, facial angiofibromas, fibrous cerebral plaque, shagreen patch, ungual fibromas, cardiac rhabdomyomas, renal angiomyolipomas | TSC2 | Everolimus (5 mg/day) | February 11, 2020: Fever (40°C), dry cough, severe asthenia, sore throat, and anorexia for 2 weeks. Treated with paracetamol, steroid nebulizer, and azithromycin changed to amoxicillin because of drug interaction with Everolimus. Everolimus was not discontinued | No | No | No | Full recovery |
| F   | 5   | Caucasian | Central Italy—at home | Severe ID, drug-resistant seizures, cortical tubers, subependymal nodules, retinal hamartomas, hypomelanotic macules, cardiac rhabdomyomas, renal angiomyolipomas | TSC2 | Everolimus (4 mg/day) | December 18–23, 2019: bronchopneumonia, treated with cephalosporin. Discontinued Everolimus. December 30, 2019: resumed Everolimus. January 12, 2020: onset of cough, rhinitis, and fever. Left pneumonia, treated with cephalosporin. Discontinued Everolimus. January 30, 2020: resumed Everolimus. February 3, 2020: cold, bronchitis, treated with cephalosporin. Discontinued Everolimus. February 17, 2020: resumed Everolimus. | No | No | No | Full recovery |
| M   | 51  | Caucasian | Northern Italy—at home (Lombardy) | Normal cognitive functioning, anxiety, seizures, cortical tubers, white matter radial migration lines, one hypomelanotic macule, facial angiofibromas, hepatic angiomyolipomas | NMI | No | January 16, 2020: onset of cough, fever (2 days), and anosmia (10 days). Treated with paracetamol | No | No | No | Full recovery |
which could expose TSC patients to increased risk of SARS-CoV-2 infection. Although the doses initially used in TSC individuals were not much lower than those used in oncology, lower effective doses have been used in clinical practice (i.e., for subependymal giant cell astrocytomas; Franz & Krueger, 2018), which could therefore have limited immunosuppressive effect. On the other hand, mTOR inhibitors showed paradoxical immunostimulatory effects by boosting T-cell response (Keating et al., 2013), and the use of low-dose Everolimus was found to decrease the infection rate in elderly volunteers enrolled in a randomized, double-blinded, placebo-controlled trial (Mannick et al., 2018). In mice studies, Keating et al. (2013) showed that rapamycin enhanced protection against H5N1 infection, and data from the 2012 Middle East respiratory syndrome (MERS) outbreak suggest that treatment of cells with mTOR inhibitors decreased MERS-CoV replication in vitro (Kindrachik et al., 2015). The hypothesis that mTOR inhibitors may be beneficial in SARS-CoV-2 infection is therefore intriguing, but additional studies are required to obtain a definitive answer. A prospective assessment of COVID-19 in TSC patients who take mTOR inhibitors for their underlying condition may shed light into this interesting question.

4.1 | Limitations

Although this preliminary study represents the first assessment of COVID-19 in patients with a rare genetic disease, it has several limitations. First, SARS-CoV-2 testing was limited in our cohort, and we cannot estimate the confirmed infection rate in TSC patients. Second, some asymptomatic patients could have been infected with SARS-CoV-2 but would have been missed due to limited testing. Finally, this study relies on patients' reports and is restricted to a small sample size.

5 | CONCLUSIONS

This rare disease cohort provides a screenshot of the presence and outcomes of SARS-CoV-2 infection among patients with TSC in Italy. Although our observations seem reassuring, physicians and patients should keep in mind that TSC patients remain at risk of contracting SARS-CoV-2. A prospective analysis is warranted to estimate the real infection rate in TSC patients and to evaluate the effects of mTOR inhibitors on COVID-19.

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CONFLICT OF INTEREST
Angela Peron, Francesca La Briola, Aglaia Vignoli, and Maria Paola Canevini received consulting fees from Italfarmaco outside the submitted work. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Angela Peron: Designed the study and wrote the manuscript; evaluated the patients and acquired the data; performed statistical analyses; critically revised the manuscript for important intellectual content. Francesca La Briola: Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. Fabio Bruschi: Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. Silvia Terraneo: Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. Chiara Vannicola: Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. Roberto Previtali: Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. Sabrina Perazzoli: Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. Emanuela Morenghi: Performed statistical analyses. Gaetano Bulfamante: Critically revised the manuscript for important intellectual content. Aglaia Vignoli: Critically revised the manuscript for important intellectual content. Maria Paola Canevini: Critically revised the manuscript for important intellectual content.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available in Supplementary Table SI.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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