

Updating the Treatment Guidelines for Patients With Tuberous Sclerosis Complex

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Target Audience Statement

This educational activity is intended for an international medical audience, excluding US physicians, specifically dermatologists, family practitioners, internists, neurologists, nephrologists, oncologists, pediatricians, urologists, nurses, and other healthcare professionals who treat patients with tuberous sclerosis complex (TSC).

Goal Statement

This activity will use clinical cases of patients with TSC to highlight important changes in the most recent diagnostic and treatment guidelines for TSC, with a goal of standardizing and improving the clinical care of patients with TSC.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Evaluate the updated consensus guidelines for diagnosing and treating patients with TSC and analyze their impact on clinical practice
- Recommend an optimal treatment strategy for patients with TSC based on the recently updated treatment guidelines
- Outline a transition plan from pediatric to adult clinical care for patients with TSC

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Dr Kingswood does not intend to discuss **investigational** drugs, mechanical devices, biologics, or diagnostics *not approved* by the European Medicines Agency.

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Updating the Treatment Guidelines for Patients With Tuberous Sclerosis Complex

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Bernard A. Zonnenberg, MD, PhD: Hello. I am Dr Bernard Zonnenberg, Internist and Medical Oncologist at University Medical Center in Utrecht, The Netherlands. I would like to welcome you to this program titled, Updating the Treatment Guidelines for Patients With Tuberous Sclerosis Complex.

I am joined today by Dr Chris Kingswood, my friend and colleague, who is a Consultant Physician at Royal Sussex County Hospital in Brighton, United Kingdom.

Program Goals

- Evaluate the updated consensus guidelines for diagnosing and treating patients with TSC and analyze their impact on clinical practice
- Recommend an optimal treatment strategy for patients with TSC based on the recently updated treatment guidelines
- Outline a transition plan from pediatric to adult clinical care for patients with TSC

TSC = tuberous sclerosis complex

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In this program, we will evaluate the updated consensus guidelines for the diagnosis and treatment of patients with tuberous sclerosis complex (TSC) and analyze their impact on clinical practice. We will also recommend an optimal treatment strategy for patients with TSC based on the recently updated treatment guidelines and outline a physician plan for pediatric to adult clinical care for patients with TSC.

We would like to start with some background on TSC and review key changes in the recently updated international consensus diagnostic and treatment guidelines.

Background

- TSC is a variable disease that can affect virtually any organ in the body.
- Most commonly manifests anatomically as benign tumors in the skin, brain, kidneys, lung, and heart
- Complex spectrum of nonanatomic abnormalities, such as mental disorders, developmental disorders, epilepsy, cognitive impairment, and psychiatric abnormalities

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Chris Kingswood, MBBS, MSc, FRCP: TSC is a complex and extremely variable disease. It can affect virtually any organ in the body. It most commonly manifests anatomically as benign tumors in the skin, brain, kidneys, lung, and heart and can lead to significant organ dysfunction.

There is also a complex spectrum of nonanatomic abnormalities such as mental disorders, developmental disorders, epilepsy, cognitive impairment, and psychiatric abnormalities.

More Common Manifestations of TSC by Age Group

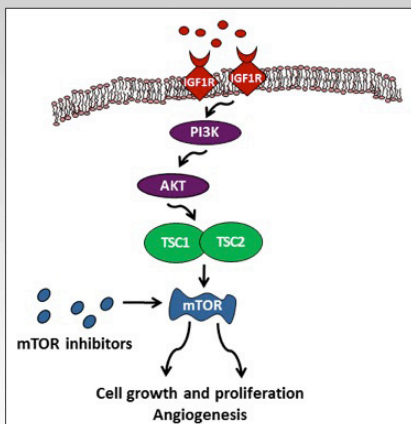
| | | |
|------------------------|---|--|
| Age ≤ 1 year | <ul style="list-style-type: none"> • Cardiac rhabdomyoma • Epilepsy • Facial angiofibroma | <ul style="list-style-type: none"> • Hypomelanotic macules • Subependymal nodules |
| Age 5-15 years | <ul style="list-style-type: none"> • Epilepsy • Facial angiofibroma • Hypomelanotic macules | <ul style="list-style-type: none"> • Renal angiomyolipoma • Subependymal nodules |
| Age 25-60 years | <ul style="list-style-type: none"> • Epilepsy • Facial angiofibroma • Hypomelanotic macules • Liver hamartoma | <ul style="list-style-type: none"> • Renal angiomyolipoma • Subependymal nodules • Ungual hamartoma |

Curatolo P, et al. *Lancet*. 2008;372(9639):657-688.

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These occur in a timeline, so that some things manifest immediately in the neonatal period, such as epilepsy, and other things take a while to develop, such as skin rash and kidney tumors.

Mechanisms of Tumor Growth in TSC



- *TSC1/TSC2* tumor suppressor genes negatively regulate the mTOR pathway
- Inactivation of *TSC1/TSC2* leads to increased mTOR activity
- mTOR inhibitors restore tumor suppressant signaling

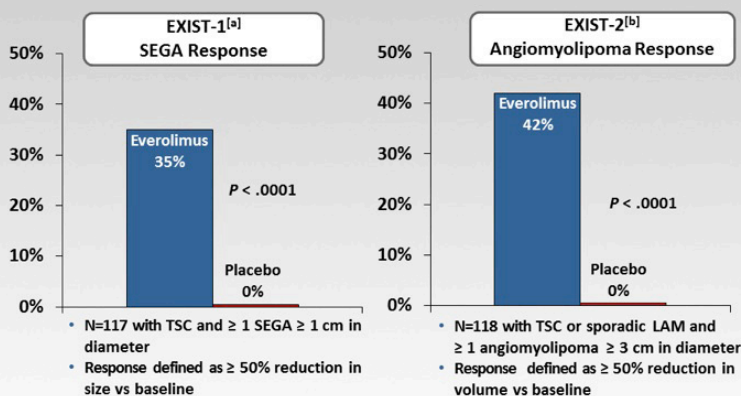
Franz DN. *Biologics*. 2013;7:211-221.



TSC is caused by mutations in 1 of 2 genes, either *TSC2* on chromosome 16, which was cloned in 1993, or *TSC1* on chromosome 9, which was cloned in 1997. The proteins of these genes make tuberlin and hamartin, which have a particular function in the cell. They turn off the growth control switch so that while they are on, the switch is off, and the cell develops normally -- it differentiates, migrates, and then dies when it needs to. If they are turned off, the cell grows and proliferates. In this genetic condition, the cells are growing all the time, which is why they form benign tumors.

It was discovered fairly recently that mTOR inhibitors, such as everolimus, will block this switch so that even cells that have the mutation can be controlled.

Everolimus in TSC: Phase 3 Clinical Trial Data



LAM = lymphangioliomyomatosis; SEGA = subependymal giant cell astrocytoma

a. Franz DA, et al. *Lancet*. 2013;381(9861):125-132.
 b. Bissler JJ, et al. *Lancet*. 2013;381(9869): 817-824.



Over the last decade, research has shown that mTOR inhibitors treat several aspects of TSC. They can decrease the size of subependymal giant cell astrocytomas (SEGAs) and can shrink renal angiomyolipomas. They can also stop pulmonary disease from progressing and decrease skin rash and angiofibromas on the face. There is also preliminary work showing that they can benefit patients with epilepsy. The mTOR inhibitor that is currently approved and licensed in Europe for the treatment of SEGAs and for renal angiomyolipomas is everolimus.

2012 International TSC Consensus Group Guidelines Updated Diagnostic Criteria

Genetic testing: presence of *TSC1/TSC2* mutations

Definite diagnosis: ≥ 2 major features or 1 major feature and ≥ 1 minor features

Possible diagnosis: 1 major feature or ≥ 2 minor features

Major Features

- Hypomelanotic macules (≥ 3 , ≥ 5 mm in diameter)
- Angiofibromas (≥ 3) or fibrous cephalic plaque
- Ungual fibromas (≥ 2)
- Shagreen patch
- Multiple retinal hamartomas
- Cortical dysplasias*
- Subependymal nodules
- SEGA
- Cardiac rhabdomyoma
- LAM[†]
- Angiomyolipomas (≥ 2)[†]

Minor Features

- "Confetti" skin lesions
- Dental enamel pits (> 3)
- Intraoral fibromas (≥ 2)
- Retinal achromic patch
- Multiple renal cysts
- Nonrenal hamartomas

*Includes tubers and cerebral white matter radial migration lines. [†]A combination of LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

Northrup H, et al. *Pediatr Neurol*. 2013;49(4):243-254.

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In 2012, a group of 79 international experts got together and drew up new international guidelines on the diagnosis, surveillance, and treatment of TSC. We pooled the world literature going back 22 years and graded the evidence to come up with the best available advice.

In the updated guidelines, we changed the diagnostic criteria so it is now based on either 2 major features or a combination of 1 major and 2 minor features. We also abolished the category of probable TSC so it is just the 2 categories of definite TSC and possible TSC diagnosis.

In addition, a new criterion of genetic testing was introduced. Now that 85%-90% of the mutations can be found, we felt that if there was a definite pathologic mutation, then that would make the diagnosis of TSC on its own. We also simplified the major and minor diagnostic criteria somewhat.

2012 International TSC Consensus Group Guidelines Updated Surveillance Recommendations

- **Lifelong surveillance is important.**
- **Key points**
 - **Brain: MRI for SEGA**
 - **Kidney: MRI for angiomyolipoma**
 - **Lungs: PFT and CT for LAM**
- **Screen for TSC-associated neuropsychiatric disorder**

PFT = pulmonary function test

Krueger DA, et al. *Pediatr Neurol*. 2013;49(4):255-265.

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In terms of surveillance, the main things that have changed are that it is recommended that someone with TSC is under surveillance throughout their life because things can happen at any point. There are some particular aspects that have changed. There should be continued surveillance for SEGAs, and people should have MRI scans every 2 years. With those MRI scans, they should also have MRIs or ultrasounds of the kidneys. MRIs are preferred because they give better definition.

Also, there should be regular surveillance for neuropsychiatric and neurocognitive problems, using the TSC-associated neuropsychiatric disorders (TAND) criteria, and regular surveillance for lung problems.

2012 International TSC Consensus Group Guidelines Updated Management Recommendations

- **Key points**
 - Infantile spasms should be identified and treated as early as possible.
 - mTOR inhibitors can be used for SEGA and renal angiomyolipoma.
- **Transition between pediatric and adult clinic should be carefully managed.**

Krueger DA, et al. *Pediatr Neurol.* 2013;49(4):255-265.

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In terms of treatment, the things that have changed are that it was identified from research that infantile spasms should be looked for and treated as early as possible, we hope within 24 hours of them starting, and the treatment of choice is vigabatrin.

For SEGA, kidneys, and lungs, there is a new treatment option with mTOR inhibitors, and we will talk about that later in the program.

The last, most important, thing is that there is often a problem with transition. When patients move from the pediatric to the adult clinic, they often get lost to follow-up, and lots of problems occur. This was recognized as a very important time, and patients should have a carefully managed transition.

Case #1: History and Current Presentation

- **History**
 - Female, diagnosed with TSC in first year of life with infantile spasms, developmental delays
 - Well-controlled epilepsy but off antiepileptic drugs for > 5 years at time of referral (age 30 years)
- **Current presentation**
 - Recurrent pneumothorax and LAM
 - Growing angiomyolipoma on ultrasound
- **No surveillance over time**

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I wonder if we could discuss the case you brought along, the patient with a SEGA?

Dr Zonnenberg: I would like to present the case of a female patient who is now 38 years old. She was referred to me about 8 years ago. She was diagnosed with TSC in her first year of life with infantile spasms and a delay in development. Epilepsy was well controlled with medication. Although she developed slowly, she was able to live independently.

She was off antiepileptic drugs for more than 5 years at the time of referral and was only treated for facial angiofibromas by laser.

The year prior to the referral, she developed recurrent pneumothorax, and a diagnosis of lymphangioleiomyomatosis (LAM) was made by pulmonologists. Because of the growing angiomyolipoma seen on the ultrasound, she was referred to my clinic.

Despite existing guidelines, she had never participated in surveillance programs prior to referral.

Case #1: Work-up and Initial Treatment

- **CT scan:**
 - Partially calcified mass at foramen of Monro on the left side
 - No ventricular enlargement, no obstruction of cerebral fluid
- **Treated for recurrent pneumothorax**
- **Embolization of renal angiomyolipomas in both kidneys**

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We obtained a CT scan of her brain, and it showed a partially calcified mass in the foramen of Monro on the left side. There was no ventricular enlargement, and no obstruction of the cerebral fluid was seen.

In the meantime, she received treatment for the recurrent pneumothorax and the embolization in both kidneys for the angiomyolipomas. After this episode, her pulmonary function decreased considerably, so she was no longer able to work.

Case #1: CT Findings



CT shows a mass consistent with a SEGA, but no obstruction.

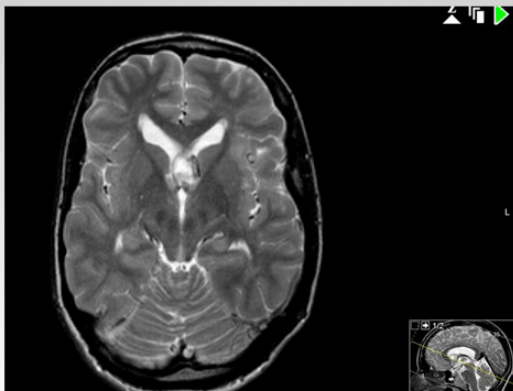
Image courtesy of Bernard A. Zonnenberg, MD, PhD.

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Here you see the CT scan; it is a large mass. The mass seen on CT is typical for a giant cell astrocytoma, but there is no obstruction of the foramen of Monro, and she continued to receive annual scans.

She was followed for a few years and recovered gradually from the pneumothorax and embolization.

Case #1: Follow-up MRI



Follow-up MRI shows an enlarged mass that expands over the midline.

Image courtesy of Bernard A. Zonnenberg, MD, PhD.

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However, MRI scans some years later showed growth of the mass in the brain. We discussed her case with the neurosurgeon, who felt surgery would be possible but might have considerable chance of postoperative morbidity. Given the pulmonary problems, general anesthesia would be an additional risk.

Because there was no sign of a block in the cerebral fluid circulation, there was not an immediate need to operate, and there was no indication for a cerebral peritoneal shunt. The neurosurgeon advised waiting until signs of internal hydrocephalus developed.

Here you see the scan. In the middle, you see the large mass growing, almost blocking the foramen of Monro on the other side. The MRI shows a large lesion in the left ventricle that expands over the midline and is one of the reasons the neurosurgeon was reluctant to operate.

Case #1: MRI After Everolimus Therapy



After 1 year of treatment with everolimus 10 mg/d, MRI shows a marked decrease in SEGA size.

Image courtesy of Bernard A. Zonnenberg, MD, PhD.

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The situation was discussed with the patient and her family, and she did not opt for surgery given the risks. Around that time, everolimus became available in The Netherlands. The treatment was discussed with the patient, and after extensive information she agreed to start on everolimus 10 mg/d. After about 1 year, MRI showed a marked decrease in size for giant cell astrocytoma as shown on this picture.

Case #1: Follow-up

- **Clinical/imaging effects**
 - Ongoing decrease in SEGA size on annual MRI
 - Facial angiofibromas gradually disappeared
 - No seizures noted
 - Embolized renal angiomyolipomas stable in size
- **Side effects: minor laboratory abnormalities and mild hypertension**

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The patient developed some minor side effects at the start of treatment, such as mucositis, but it disappeared gradually. The annual MRI scan showed an ongoing very slow decrease in size of giant cell astrocytoma. Also, the angiofibromas on her face disappeared gradually. No seizures have been observed anymore, and the angiomyolipomas in the kidney that were embolized 8 years ago are still stable in size, although they show an increased fat content.

Currently, the only side effects are minor laboratory abnormalities and raised blood pressure. She receives a phosphate supplement for low serum phosphate and an angiotensin-converting enzyme (ACE) inhibitor for her hypertension. Although an ACE inhibitor in combination with everolimus is not recommended always, it is usually very well tolerated by most patients.

Case #2: History and Current Presentation

- **History: female, age 33 years, presented with renal bleed, underwent emergency embolization: first diagnosis of TSC**
- **Other features of TSC: 3 white macules, facial angiofibromas, ungual fibromas, a cortical tuber, some subependymal nodules; typical LAM cysts on high-resolution chest CT**
- **No neurocognitive problems**
- **No family history of TSC**

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Let us discuss the case you brought of a patient with renal angiomyolipoma.

Dr Kingswood: The woman I want to talk about was not known to have TSC and was not diagnosed until she was an adult. At age 33 years, she presented with a serious, life-threatening renal bleed. The bleeding point was embolized as an emergency. The bleeding stopped, and she recovered well.

It was then noted that she had facial rash, angiofibroma to white macules, some unguis fibromata, and, on MRI scan, a cortical tuber with some subependymal nodules, so she met criteria for a definite diagnosis of TSC.

She had also developed, over the years, hypertension, hypothyroidism, and later-onset asthma. Her pulmonary function tests postbronchodilator improved, but on a high-resolution chest CT to look at her lungs, she did have early pulmonary LAM with typical lung cysts.

She did not have any neurocognitive problems. She is married, has 2 sons who are both unaffected by TSC, and she has no family history herself. She is taking thyroxine, lisinopril for hypertension, salbutamol for the asthma, and some steroid inhalers.

Guideline Recommendations

- **MRI of the abdomen to assess angiomyolipoma and renal cystic disease every 1-3 years**
- **Assess renal function and blood pressure at least annually**
- **Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage; avoid nephrectomy**
- **mTOR inhibitor is first-line therapy for asymptomatic, growing angiomyolipoma > 3 cm**
- **Selective embolization or kidney-sparing resection are acceptable second-line therapies for asymptomatic angiomyolipoma**

Krueger DA, et al. *Pediatr Neurol.* 2013;49(4):255-265.

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She had an MRI of the abdomen to assess progression nearer to once every 3 years rather than every year at the hospital before she was referred in. She had an assessment of her renal function and blood pressure annually, which is standard protocol.

In the international guidelines, we recommend MRIs every 1-3 years as well as annual renal function tests and blood pressure measurement in a patient known to have angiomyolipomas. If there is a concern about the renal lesions growing, we repeat the scans more often.

The international guidelines also came out strongly in favor of embolization for emergency bleeding, because that is the safest thing to do in an emergency. It is better than surgery, as surgery often results in nephrectomy in the setting of an acute bleed. Following embolization, prophylactic high-dose steroids should be used to decrease embolization syndrome.

However, in the case of people with angiomyolipomas that are > 3 cm and still growing, where there is a significant risk for future bleeding, preemptive treatment is recommended.

On the basis of the EXIST-2 study and the license of everolimus, it was recommended that first-line therapy should be an mTOR inhibitor. Other things, such as embolization or kidney-sparing surgery, should be second line because they risk compromising renal function. The one thing we want to do long term is preserve renal function in these patients.

Case #2: Treatment

- MRI scan showed 4 large angiomyolipomas, total volume of 159 mL
- After 6 months of everolimus 10 mg/d:
 - Kidney lesions shrank to 25% of original volume
 - Glomerular filtration rate improved
 - Facial rash improved by 90%
- After 24 months, everolimus dose was reduced to 5 mg/d because of side effects; total volume of angiomyolipomas down to 34 mL
- Long-term reduction in angiomyolipoma size with everolimus consistent with data from EXIST-2 clinical trial^[a]

a. Bissler JJ, et al. *Lancet*. 2013;381(9869):817-824.

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In this case, after embolization, she did not have any angiomyolipomas > 3 cm at first, and then she had intermittent follow-up.

By 2010, a repeat MRI scan showed that she had 4 angiomyolipomas that were much bigger -- one was 42 mm in diameter, one was 46 mm, one was 68 mm, and one was 78 mm; there was a total volume of 159 mL of the largest angiomyolipomas.

To deal with those preemptively in the old days, we would have had to do 4 embolizations, which would have significantly affected her kidney function. We opted after discussion with her to go with treatment with an mTOR inhibitor, and she was prescribed everolimus 10 mg/d.

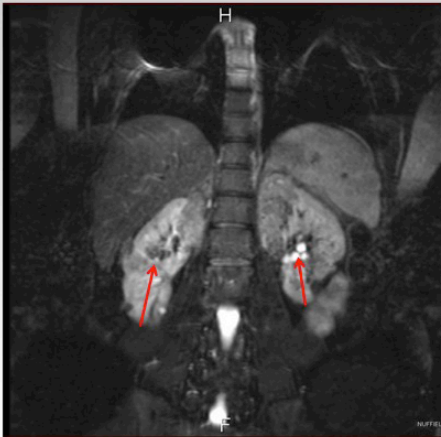
It was very successful. By 6 months, her angiomyolipomas had shrunk down to 25% of their previous volume. She had had no further bleeding. Also, over that first 6 months, her glomerular filtration rate improved from 58 mL/min to 67 mL/min.

She did have some minor adverse events. She had a couple of episodes of mouth ulcers, but they responded well to treatment. She had some menorrhagia, which was probably due to her uterine fibroids rather than the treatment. She had an episode of pyelonephritis; we know from the EXIST-2 and EXIST-1 studies that there may be increased infection in patients on mTOR inhibitors, but it is not really a big problem. She had some headaches, which may have been treatment related.

Then she had a positive side effect of improvement in her facial rash, which, like your patient, progressively improved until it was 90% cleared.

Because of the infections, menorrhagia, and mouth ulcers, by 24 months, we reduced her dose of everolimus to 5 mg. After that, she had no further side effects. At 24 months, she had continuing improvement in her angiomyolipomas, and the total volume is now down to 34 mL.

Case #2: MRI Prior to Everolimus Treatment



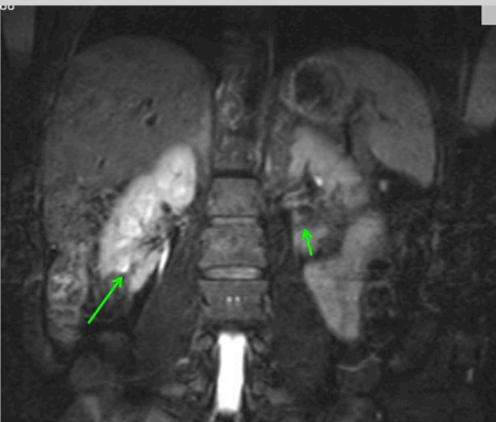
Large, vascular renal angiomyolipomas are visible on MRI.

Image courtesy of Chris Kingswood, MBBS, MSc, FRCP.



These are a couple of pictures. This is before she started therapy, and I have marked the 2 largest angiomyolipomas at the bottom of each kidney. As you can see, they are quite vascular and quite worrying.

Case #2: MRI After Everolimus Treatment



After treatment with everolimus, angiomyolipomas are markedly smaller and less vascular.

Image courtesy of Chris Kingswood, MBBS, MSc, FRCP.



After therapy, not only have they shrunk, but also they are much less vascular. Again, 2 years down the line, she has not had any further bleeding.

Case #2: Key Points

- **Effect maintained despite dose reduction**
 - Lesions shrank by 79%, no bleeding after 26 months
- **Manageable adverse events**
- **Renal function stable or better**
- **Welcome improvement in skin rash**
- **Lung function may be stabilized**
- **Monitoring MRI often more accurate than ultrasound**

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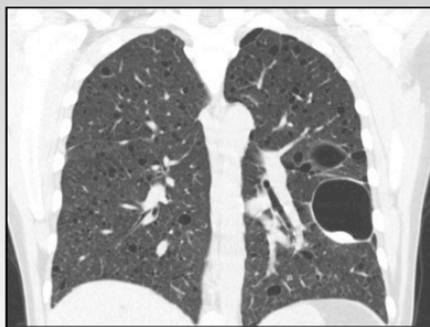
The main points of her case are that the effectiveness of the therapy is maintained despite the dose reduction. Angiomyolipomas have now shrunk by 79%. She has had no bleeding.

The adverse events she did have were minor and easily managed. Her renal function is at least stable and probably better. She had a side benefit of welcome improvement in her skin rash.

We do not know yet about her lung function; certainly she has early pulmonary LAM. We know that mTOR inhibitors can stabilize that, so presumably the everolimus will too.

The previous monitoring that she had had prior to her referral to our center had mainly been ultrasound, which had given unclear pictures. So that is another practice point -- that MRI scan is, if it is practical, a much better technique for surveillance.

LAM in Patients With TSC



- **Most common in women, seen in adolescence and later**
- **Large cysts compromise lung function**
- **High-resolution CT scans recommended every 2-3 years in patients with LAM**
- **Scan every 5-10 years if no signs are noted in adolescence**
- **Additional data are needed to determine optimal use of mTOR inhibitors in early LAM**

Krueger DA, et al. *Pediatr Neurol.* 2013;49(4):255-265.
Image courtesy of Bernard A. Zonnenberg, MD, PhD.

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I wonder in the last few minutes whether you could describe some other common features of TSC?

Dr Zonnenberg: Yes, of course. It is a complex disease, so we have to consider other anatomic disorders.

As to the lungs, as you already mentioned, involvement of the lungs is often overlooked and occurs in about 20% of all females. It is a serious problem. It does not occur in youth but in adolescence or a little bit later. The CT scan I already showed you showed how it looks.

Patients with TSC should have an adequate high-resolution CT scan of the thorax. Adolescents should have one at about 16 or 17 years of age to look for the first signs of LAM. If present, recommend follow-up of progression at regular intervals, annual pulmonary function tests, and a detailed pulmonary history; in cases of recurrent coughing, patients may benefit from inhaled corticosteroids or bronchodilators.

Here you will see the patient I already showed you, with large cysts. You can imagine that these lungs are not as functional as normal lungs, and if you are young and you end up with these lungs, it will be very difficult to live long, so something must be done to stop it.

The guidelines suggest that patients with characteristics of LAM should be followed at least every 2 or 3 years with a high-resolution CT scan; if the patient does not show LAM in adolescence, it is advised to perform a CT scan every 5 or 10 years.

Currently, the data are somewhat premature to justify use of an mTOR inhibitor early in LAM in TSC patients. However, the data currently available in non-TSC populations are showing very encouraging results with mTOR inhibitors, so they might be considered.

TSC-Associated Neuropsychiatric Disorder

- **Complex interactions between brain dysfunction and behaviors**
- **High incidence of neurocognitive deficits**
- **Neuropsychological and psychiatric testing recommended during childhood at every phase of development as well as in early adulthood (18-25 years)**
- **Patients may benefit from neuropsychological and psychiatric testing later in adulthood**
- **Cognitive problems and psychiatric disorders should be dealt with appropriately**

Krueger DA, et al. *Pediatr Neurol.* 2013;49(4):255-265.

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The last and perhaps most important thing is TAND, the TSC-associated neuropsychiatric disorders. It describes the complex interaction between brain dysfunction and behaviors. These problems deserve much more systematic attention. Given its high incidence and the social problems with TSC patients and their family members, these symptoms should be addressed accordingly.

Patients should receive regular neuropsychological and psychiatric assessments during childhood and at every phase of development as well as in early adulthood, say 18 to 25 years. The patient may also benefit from neuropsychological or psychiatric testing later in adulthood, so it should never be neglected. Of course, any cognitive and psychotic disorders that are not typical for TSC should be dealt with properly according to the current standards.

Epilepsy

- **Changes in epilepsy and behavior may be due to growth of SEGAs, renal angiomyolipomas, or non-TSC-related abnormalities.**
- **Consider somatic abnormalities before changing antiepileptic drugs, particularly among patients with a mental handicap.**

Krueger DA, et al. *Pediatr Neurol.* 2013;49(4):255-265.

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Last, but not least -- epilepsy. It is important to note that a change in epilepsy and behavior may be caused by changes in the growth of SEGAs, renal angiomyolipomas, or other non-TSC-related abnormalities. Before changing antiepileptic drugs, it is important to look for somatic abnormalities, particularly among patients with a mental handicap.

Transitioning From Pediatric to Adult Care Suggested Best Practices

- **Introduce the physician coordinating adult care into the pediatric clinic.**
- **Make sure that the physician will be managing the case for a considerable amount of time so as to avoid frequent changes.**
- **Change in physicians is particularly challenging for those with autism spectrum disorders and can interrupt the surveillance program.**
- **Introduce patients to the differences in pediatric and adult care settings so they can adapt more easily.**
- **Limit the number of visits to improve acceptance to the new care environment.**

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Another thing that troubles many patients is the transition from pediatric to adult care.

There are no set guidelines for how to transition, so you have to look to the most important points. You have to introduce the physician who will be coordinating the TSC patient in the adult clinic. They should be involved late in pediatric care, so the patient and the parents become familiar with the person who will take over.

Make sure the physician will be able to continue managing the case because it takes a considerable amount of time to get acquainted with each other. There is a large number of TSC patients with autistic spectrum disorders, and they are very vulnerable to changes and other doctors, so this can jeopardize the surveillance program. And once patients are out of the surveillance program, it is very difficult to regain trust in the physician again to get optimal surveillance done.

I always explain that the hospital environment for adults is much larger and much more noisy than the children's hospital. It is a different setting, and it is important to explain this to the parents and the patients a number of times so they can adapt to this change.

Of course, limit the number of visits. For instance, combine the MRI with lab tests and visiting the physician. If the physician will be able to see the patient in the waiting room prior to the MRI, this would improve acceptance to the new hospital environment. It will help considerably.

I will give the last word to you in our last few minutes.

Summary

- **New guideline recommendations focus on the importance of life-long surveillance and a multidisciplinary approach to care.**
- **New treatment options are available for patients with SEGAs and renal angiomyolipomas, which are key features of TSC.**
- **Ongoing studies will better define the role of mTOR inhibitors in patients with other features.**
- **Transition of the patient from care as a child to care as an adult is important to ensure effective treatment and surveillance.**

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Dr Kingswood: In conclusion, our new recommendations are that there should be comprehensive surveillance of patients with TSC, and this should be carried out with a multidisciplinary approach because there are many different sorts of problems. But there should be one person coordinating the care holistically and making sure that patients get what they need.

It is important to note that there are some new treatment options available, although indications and how we use them will evolve as time goes on.

Lastly, a patient with TSC needs lifelong care, from childhood through to adulthood. We need to set up mechanisms in order to continue to look after the patient.

Thanks, Bernard, for joining us today. And thank you, the audience, for viewing this program. We hope that you found it interesting and useful and helpful in your clinical practice.

This transcript has been edited for style and clarity.