Drug Therapy for LAM

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(Drug) Therapy For LAM

- **Disease Modifying**
  - MTOR inhibitors (sirolimus, everolimus)

- **Symptom Management**
  - Oxygen
  - Rehab/exercise
  - Antidepressants/Anxiolytics
  - Inhalers
  - Lung transplant
Roadmap

- Sirolimus
  - What is it?
  - Why in LAM?
  - Nuts and Bolts
- Old therapies
- Future therapies
Sirolimus

- **Rapamycin = Rapamune = Sirolimus**
- First of a class of medications called mTOR inhibitors
- Discovered in a soil sample on Easter Island – initially used as an antibiotic
- Now most common use is as a immunosuppressant in patients who have had transplants
- Also used in heart stents to stop them from getting clogged and as a cancer therapy (kidney cancer and some lymphomas)
mTOR is an enzyme that lives in human cells and is part of a long and complex chain of interactions that control cell growth.

Blocking mTOR should reduce the growth of cells that are rapidly dividing.

Doesn’t kill the cells – just slows growth.

Taveira-DaSilva and Moss. Rev Port Pneumol. 2012;18:142-4
Sirolimus

- Other mTOR inhibitors
  - Everlimus (Affinitor)
  - Temsirolimus
SIROLIMUS IN LAM
Why sirolimus?

- Tuberous sclerosis complex is a genetic disorder with known abnormalities of TSC1 and TSC2 genes that lead to abnormal TSC1 and 2 proteins.
- Some patients with TSC develop LAM.
- We know that TSC1 and 2 stimulate the mTOR enzyme.
- So the theory was if you block mTOR perhaps you would effect LAM.
CAST Trial

- Cincinnati Angiomyolipoma Sirolimus Trial (CAST)
  - Looked at the effect of taking sirolimus for a year on the size of the AMLs (kidney growths)
CAST

Bissler et al. NEJM. 2008; 358: 140-151.
While not the focus of the study, they found that the FEV1 and FVC improved while on therapy.
MILES Trial

Other Effects

- Improves chyloous effusions
- Improves AMLs
- Improves chyloous ascites

Guidelines for therapy

- FDA approved sirolimus for the treatment of LAM in 2015
- ATS/JRS Guidelines for the Diagnosis and Management published September 2016

MILED trial – should we start it earlier?

Recommendation 1a
For patients with LAM with abnormal/declining lung function, we recommend treatment with sirolimus rather than observation (strong recommendation based on moderate-quality evidence).
Remarks. Abnormal lung function is defined as an FEV₁ less than 70% predicted. The goals of sirolimus therapy are to stabilize lung function, improve functional performance, and improve overall quality of life.

Recommendation 1b
For patients with LAM with symptomatic chylous fluid accumulations, we suggest treatment with sirolimus before invasive management (conditional recommendation based on very low-quality evidence).
Remarks. Chylous fluid accumulations include chylous effusions and chylous ascites. Invasive management refers to interventions such as intermittent percutaneous drainage and insertion of indwelling drainage devices. Importantly, chylous fluid accumulations may require several months to respond to mTOR inhibitors and can recur after treatment cessation.
SIROLIMUS – NUTS AND BOLTS
Sirolimus: How do I take it?

- Take this medicine with or without food, but be consistent
  - Always take with food or always take on an empty stomach
- To gain the most benefit, do not miss doses
- Swallow the pill whole – don’t crush or chew
- Store the tablets at room temperature
- Keep in the blister pack until ready to take
- There is a liquid form of the medicine if you need it but the dose is not always equivalent
What do I do if I miss a dose?

- Take a missed dose as soon as possible
- If it almost time for the next dose, skip the missed dose and return to your regular schedule
- Do not take a double dose or extra doses
- Talk with your healthcare provider before making any changes to dosing
What are the precautions when taking this medicine?

- Inform your healthcare provider of
  - All medicines that you are already taking
    - Prescribed, homeopathic and supplements
  - Any new medications prior to starting them
- Avoid grapefruit and grapefruit juice
- Use non-estrogen based birth control
  - Sirolimus can harm a fetus
- May need to modify medication with any procedure and/or injury
  - Wound healing issues
- May need to come off if you are listed for transplant – discuss with your center
Sirolimus: Side Effects

- Fairly Common
  - Oral ulcers*
  - Edema/swelling
  - Diarrhea
  - Nausea
  - Acne like rash
  - High triglycerides and/or cholesterol
- Less common but happen
  - Abnormal periods
  - Ovarian cysts
  - Abnormal liver function tests
  - Kidney dysfunction

- Less common but worrisome
  - Higher blood sugars
  - Higher blood pressures
  - Increased risk of infection
  - Poor wound healing
  - Increase risk of cancer
Sirolimus: Oral Ulcers

- Frequent
- Often dose related and an early complication
- Cause: Immune related not infectious

**Treatments**

- Saline (salt water) rinses with pinch of sodium bicarbonate
- Chorhexidine gluconate mouthwash
- Benzydamine mouthwash
- Topical steroid therapy
- Intra-lesional steroid injections
- Systemic steroid therapy
Sirolimus: What to monitor?

- Changes in your reason for treatment
  - I.e. Shortness of breath, lung function, pleural effusion, ascites
- Check blood pressure and heart rate regularly
- Check blood work regularly
  - Complete blood count, serum creatinine
  - Cholesterol and other lipids
  - Liver function tests
  - Urinalysis (protein)
Sirolimus: Drug Levels

- **Therapeutic drug levels:** 5 - 15 ng/ml
- The level is measured as a trough level
  - That means we want to measure it 20-24 hours after your last dose and then you should take your next dose after having the blood drawn
- The dose you need will be determined according to the trough level
- This drug is metabolized very slowly by the body so it takes several days for changes in the dose to be accurately reflected in the blood level
Sirolimus: Drug Interactions

- Many medicines alter the sirolimus level
  - Tell your health care provider if you are taking any new medicines or if you have stopped taking a current one

- Calcium channel blockers
  - nicardipine, verapamil

- Antifungal agents
  - clotrimazole, fluconazole, itraconazole, voriconazole

- Macrolide antibiotics
  - clarithromycin, erythromycin

- Other antibiotics
  - Rifabutin, rifampin

- Gastrointestinal motility drugs
  - cisapride, metoclopramide

- Anti-seizure meds
  - carbamazepine, phenobarbital, phenytoin

- Natural remedies
  - St. John's Wort (hypericum perforatum), echinacea

- Foods
  - Grapefruit juice
Generic versus Brand Name

- Some recent concerns within community about brand versus generic sirolimus
- In general FDA has very high standards for generics
  - Same active ingredient, strength, dosage, form
  - Same bioavailability
  - Same safety and preparation standards
- No direct studies comparing generic and brand with sirolimus but do have those for other drugs where dosing is very important and no real differences detected to date
  - i.e. Blood thinners, seizure medications, other immune suppressants
- There was a recall of some sirolimus pills made by Dr. Reddy company due to impurities in the pills – just some batches of the pills
- So in general generics probably just fine but should pay attention whenever switch formulations to things like blood levels
Sirolimus: Vaccinations

- Sirolimus may reduce your ability to mount a good immune reaction to vaccines
- Therefore, have any vaccines that you are due for prior to starting the drug
- Once you are on the drug you can still do many but not all vaccines
  - Those that come from inactivated bacteria and viruses are okay
    - Influenza
    - Pneumococcal
  - Those that are from live viruses you should not take
    - Shingles
    - MMR
OTHER THERAPIES
Guidelines recommend against these in most LAM patients (exceptions may exist):

- Doxycycline
- Hormonal therapies
Potential new therapies

- No other drugs are approved
- Several are in various stages of clinical trials
  - Hydroxychloroquine
  - Simvastatin
  - Saracatinib
  - Celecoxib
  - Imatinib
- Some are intended as monotherapy, some in combination
- Like all experimental therapies – some will work and some won’t, don’t try on your own but enroll in studies!!!
Conclusions

- Sirolimus is the only FDA approved therapy to modify the disease course in LAM.
- It has common but generally manageable side effects.
- To be most effective it’s a team effort between the patient and the doctor.
  - Drug interactions
  - Dosing issues
  - Side effects
  - Monitoring toxicity and effectiveness
- When used appropriately in the right patients it appears to be effective in many.
- It is “cytostatic” not “cytotoxic” so the search for a cure is ongoing.
- We need those who qualify to enroll in studies so we learn more.