Preventing Alzheimer's Disease with Rapamycin

Alan S. Green, M.D. is one of the nation's only doctors who practices anti-aging medicine using rapamycin. Dr. Green has expanded his practice into the prevention of Alzheimer's disease, and believes that rapamycin may be one of the best means available to prevent it, especially in high-risk patients, and he's written a comprehensive website on this use of rapamycin. In the service of getting the word out and explaining this important concept, we again interview Dr. Green.

P. D. Mangan: Why did you set up your new website, Prevention of Alzheimer's Disease in APOE4 Carriers?

Alan S. Green, M.D.: The most vulnerable medical group today are the 20 million Americans in the 40-70 age group who are APOE4 carriers. They are at high risk of Alzheimer's disease.

Since 2010, there have been studies with excellent mouse models of AD with human genes for AD showing rapamycin will prevent AD. The most important study was a 2015 study in which mice were given human genes for APOE4.

It seems like the attitude in clinical medicine is what happens in the research laboratory stays in the research laboratory, at least as far as generic drugs like rapamycin are concerned.

Many people are having genetic testing and finding out they are APOE4 carriers. The APOE4 community need three things. (a) The need convenient access to the best current scientific information. (b) They should be able to see a physician who's main interest is providing the best prevention plan and (c) they need access to what looks like, in the basic science laboratory, the

most effective medicine in preventing AD in APOE4 carriers, even if that use is “0ff-label”.

PDM: Can you briefly summarize your website?

ASG: The website provides a current understanding of the etiology and development of AD in APOE4 carriers. The websites highlights all the basic research and mouse studies showing rapamycin will prevent AD in APOE4 carriers. The website discusses risk and lifestyle required to lower that risk. It lets people looking for help know there is a medical office with the primary interest of prevention of AD in APOE4 carriers, using all the tools currently available, even if medication is “off-label”.

PDM: You are offering rapamycin “off-label” prior to human clinical trials proving that rapamycin prevents AD in humans in APOE4 carriers; when do you think traditional medicine will have results from human clinical trials showing rapamycin is effective to prevent AD?

ASG: My opinion is that is at least 10 years down the road. The problem with that is many APOE4 carriers don’t have 10 years to wait. Even if rapamycin works in early stage to prevent AD; it will not work in late stages. Prevention is absolutely required because chance of cure of established AD is extremely remote possibility.

PDM: How will you know if the treatment is working?

The best test is PET scans to study any changes in cerebral blood flow.

However, we can also follow progress with psychological testing to see small impairment or improvement in memory. Decline in memory is a very sensitive early indicator of cognitive decline.

PDM: With the current interest in prevention of AD, why has progress with rapamycin been so slow ?

Rapamycin is a generic drug. There is no pot of gold at end of the rainbow for rapamycin.

PDM: Since our last interview in May 2017, how have you been doing? Do you still feel that rapamycin has been crucially important in your return to health?

ASG: I will turn 75 this February and have now been on weekly rapamycin for 2 years. I have not had any significant side-effects from weekly rapamycin. As regards aging, I feel like I am now in “remission”. I am very happy about the function of my brain and heart. I credit Mikhail Blagosklonny and rapamycin for giving me a new lease of life. **I consider rapamycin the most important new drug since discovery of penicillin 90 years ago.** [Emphasis added – PDM]. The failure of the medical community to have widespread use of rapamycin to prevent age-related diseases including AD is an enormous loss to older people.

PDM: How is your rapamycin-based practice for prevention of age-related

diseases going ?

ASG: For the past eight months, I have treated a fairly small number of patients. The remarkable thing is that average distance from where patients live to my office is probably around 1000 miles. I have seen patients from UK, Canada, Cayman Islands, and about 20 states including California, Texas, Florida, Massachusetts. Most patients fly to NYC. They are a remarkably knowledgeable group.

Weekly rapamycin is very well tolerated and only a few patients have had any side-effects.

PDM: As a physician in the anti-aging field, what do you consider the most important development is for 2017?

ASG: Matt Kaeberlein's experiment with old companion dogs. He gave old dogs intermittent rapamycin for 3 months and showed improvement in cardiac function. Some of the dog owners said their old dogs were running around like puppies.

[This short video shows the remarkable results of a dog on rapamycin – PDM]

However, in my opinion, for the most part, the anti-aging field is dominated by quack medicine and junk science.

PDM: How can people discern real science and results in treating aging?

ASG: Mikhail Blagosklonny said aging and age related disease were connected like smoke and fire. This means an anti-aging drug should both extend the lifespan of all different organisms tested including yeast, flies, worms, and mice; but should also prevent almost all age-related disease including cancer and heart disease.

PDM: How big an effect do you think rapamycin will have on human lifespan ?

Rapamycin has one effect, it decreases mTOR. Elevated mTOR appears to play a very major role in age-related disease. I expect rapamycin will have a huge effect on preventing age-related disease and keeping people healthy in their seventies and eighties. Other than that, we will have to wait another 20 or 30 years to see the full impact of lowering mTOR.

PDM: Getting back to your new website, what should APOE4 carriers know?

ASG: First they need to understand their real risk and the things they should do to lower their risk.

Everybody knows APOE4 carriers are at increased risk; but the increased risk is greatly minimized by how the numbers are presented. Overall APOE4 carriers have a 3.2 fold increased risk; but their mean age of onset is 10 years sooner than non-E4 carriers. In the 60-69 age group, they have a 5.6 fold increased risk, in the 70-79 year age group a 4 fold increased risk. The increased risk is only 1.7 fold in the 80-89 age group. When averaged

together the large number of cases of AD in 85 plus age group who are non-E4 carriers with the AD cases in E4 carriers in the younger age group, it creates a false impression. It is not that the lifetime risk in non-E4 group is 9% and lifetime risk in E4 group is 29%, it is the 10 years sooner mean age of onset that makes the huge difference in impact.

The impact of lifestyle on APOE4 carriers is very large; in contrast, lifestyle seems to have a small impact in non-E4 carriers as regards risk of AD. Any statement about lifestyle as regards risk of AD in general population is worthless and dangerously misleading as regards APOE4 carriers.

There are very many dramatic examples of this: High saturated fat diet increases risk of E4 carriers 11 fold; but has no significant increased risk for non-E4 carriers. Frequent alcohol intake increases risk 7 fold vs never drinkers in E4 group; but actually lowers risk in non-E4. Overweight, obesity, diabetes greatly increase risk in E4 carriers compared to non-E4 carriers. The benefits of physical activity is much greater in E4 group. A sedentary lifestyle with overeating, eating large amount of red meat, overweight combined with moderate alcohol intake might be reasonably safe for non-E4 carriers; but very high risk for APOE4 carriers. Information reported might be correct for non-E4 carriers; but very different for E4 Carriers. Therefore, E4 carriers they must know their E4 status so they can take appropriate steps to minimize their risk.

PDM: What basic science should they know?

The website deals with this in two sections; Basic Science and Mouse studies.

AD in APOE4 carriers is a 2 hit disease. (Zlokovic theory) The first hit is deterioration of the vascular system. The 1st hit develops decades before the second hit and decades before first onset of cognitive changes. PET scans of cerebral blood flow shows deterioration starts in the 20-39 year age group in E4 carriers. The damage to cerebral blood flow results in accumulation of amyloid. The accumulation of amyloid then triggers the second hit which has been called the amyloid cascade. The second hit includes accumulation of hyperphosphorylated TAU, which is extremely damaging to nerve cells. The accumulation of amyloid is first noted age at mean age 56 in E4 carriers, compared to age 76 in non-E4 carriers.

The 2 hit theory, shows that deterioration of vascular system precedes hit 2 and amyloid cascade by decades. This provides excellent opportunity to prevent deterioration of vascular system in E4 carriers.

APOE4 is not a mere risk factor; but rather the cause. The specific etiology on a molecular level is that in APOE4 carriers the ApoE4 lipoprotein fails to combine with transport protein LRP1. [weak ligand] This results in activation of proinflammatory substance CypA which then activates the usual suspect NF-kB which activates MMP9 which then breaks down BBB (blood-brain barrier). The important thing to understand is that there is a specific pathway and rapamycin blocks this pathway which prevents damage to BBB and cerebral blood flow.

The Mouse studies section looks at 8 mouse studies with transgenic mice with human genes for AD. The most important study was a 2015 study in which mice were given human APOE4 genes. [Spoiler alert]. In every study rapamycin prevents development of AD like pathology and cognitive deficits.

The basic science details very many precise steps in two hit development in which rapamycin lowers mTOR and blocks the various steps.

Examination of the human brain from APOE4 carriers with AD, shows these same finding in the mice who were given human APOE4 genes are also present in the human brain.

PDM: What do we know about human APOE4 carriers that suggests rapamycin will prevent development of AD in this group?

ASG: Everything that raises mTOR in human APOE4 carriers, very much increases risk of development of AD. High calorie diet, overweight, obesity, diabetes all increase mTOR and all very much increase risk of development AD. Things like exercise and low calorie diet which reduce mTOR, lower risk of AD.

PDM: What methods are some APOE4 carriers now using to decrease their risk?

ASG: Many of them are using a regime that includes fasting, avoiding sugar and red meat. These are all methods to lower mTOR.

PDM: Would you expect rapamycin to protect against AD in non-E4 carriers?

ASG: Yes. Rapamycin would be expected to protect against AD in non-E4 carriers by the following mechanism:

Rapamycin protects against hyperphosphorylation of Tau by many mechanisms as discussed in the Tau section. Tau is major player in AD.

Rapamycin would prevent accumulation of amyloid by increase in autophagy.

Increase in amyloid causes increases in mTOR which increases Tau, rapamycin blocks this step.

Rapamycin would help preserve cerebral blood flow by decrease in CypA[Symbol]NF-kB[Symbol]MMP9 pathway leading to breakdown of BBB which develops in old age due to very marked age-related decrease in LRP1.

Rapamycin increases cerebral blood flow by increased nitric oxide.

The mean age of AD in non-E4 carriers is 85. Starting rapamycin at age 75 should be helpful to prevent AD in non-E4 carriers. This is in contrast to E4 carriers who, in my opinion, should probably start rapamycin at age 45 to prevent deterioration BBB and cerebral blood flow.

PDM: What is the effect of rapamycin on the normal aging brain?

Based upon mouse studies rapamycin might prevent memory decline. Age 60 is probably a good age to start to protect the brain from age-related

memory decline.

Rapamycin increases catecholamines in the mid-brain which may prevent against age-related depression.

PDM: Many people have asked me whether rapamycin might impair muscle anabolism (growth) in resistance training. What do you think?

ASG: It might. mTOR builds large muscles.

However, rapamycin would help prevent against sarcopenia (muscle wasting in aged) by decreasing inflammation.

Rapamycin may also help preserve muscle strength by an increase in number of mitochondria by preserving mitophagy.

[See below for more on this. – PDM]

PDM: What effect would you expect of rapamycin on testosterone and sexual performance ?

ASG: Intermittent rapamycin would *not* affect testosterone levels in contrast high levels daily Rapamycin.

Rapamycin causes an increase of catecholamines in midbrain which might increase sexual interest.

Rapamycin increase in activity of NOS (nitric oxide synthase) and increase in nitric oxide could improve sexual performance.

PDM: Insulin resistance is an important cause of pathology in the diseases of civilization; what's the relation of insulin resistance to AD?

ASG: You are correct. Major cause of civilization-related disease is through insulin resistance / high insulin / high mTOR pathway. Insulin resistance causes high insulin levels and high mTOR. High mTOR is then the major driving factor in most age-related disease and AD.

Insulin resistance should be viewed as a very serious disease with diabetes just one of the complications of insulin resistance.

Addendum: Rapamycin and muscle

Dr. Green above noted several effects of rapamycin on muscle, some of them opposing each other, so here's some more information.

Rapamycin doses sufficient to extend lifespan do not compromise muscle mitochondrial content or endurance

> Rapamycin-treated mice had endurance equivalent to that of untreated controls, and isolated, permeabilized muscle fibers displayed similar rates of oxygen consumption. We conclude that the

> doses of rapamycin required to extend life do not cause overt mitochondrial dysfunction in skeletal muscle.

So, muscle endurance is not compromised.

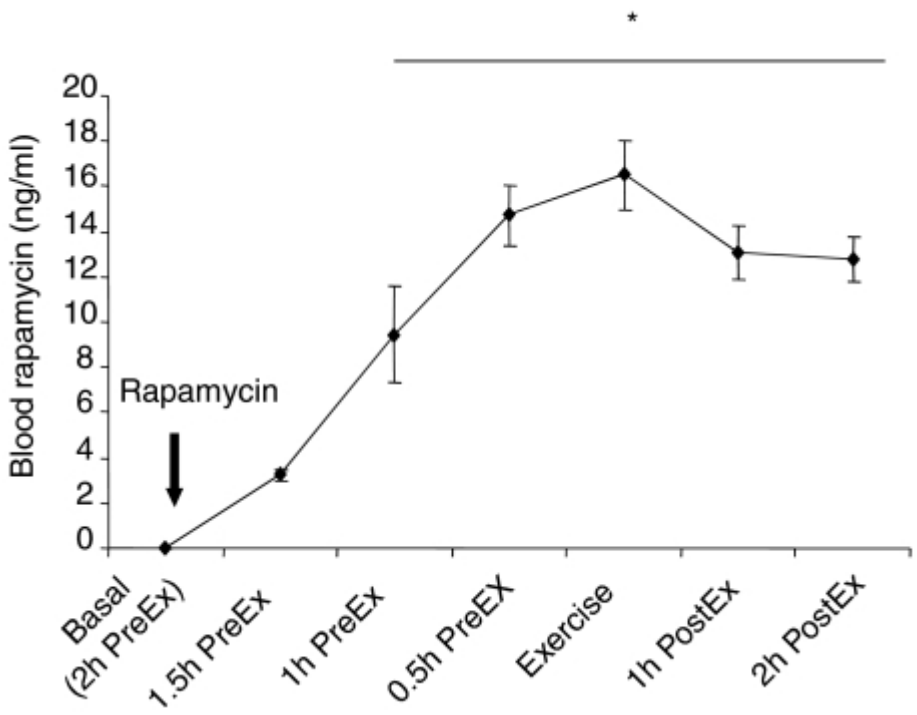
In yeast, life extension by rapamycin seems linked to increased mitochondrial gene expression.

However…

Rapamycin administration in humans blocks the contraction-induced increase in skeletal muscle protein synthesis

> Here we show that rapamycin treatment blocks the early (1–2 h) acute contraction-induced increase (~40%) in human muscle protein synthesis. In addition, several downstream components of the mTORC1 signalling pathway were also blunted or blocked by rapamycin.

Comment: The subjects in this study took a huge dose of rapamycin, 12 mg, immediately before a workout. Below is concentration of rapamycin in blood by time.



Insulin response was blunted during and after exercise compared to controls, and muscle protein fractional synthetic rate in rapamycin treatment was also blunted.

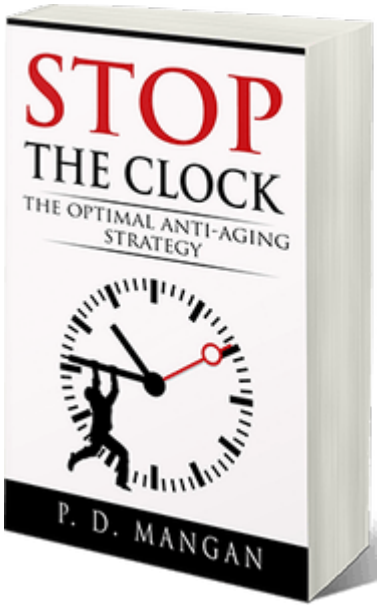
The type of rapamycin treatment that Dr. Green advocates and prescribes is once weekly and at a much smaller dose. An otherwise healthy man aged about 60 might take 2 mg rapamycin weekly, only 1/6 the amount in the above experiment that blunted muscle synthesis following resistance training.

Here's a case where timing would be very important. Someone could take rapamycin but do strength training away from the dose, perhaps more than 2 days later. As I understand it, the type of mTOR activation that promotes aging is *chronic* activation. An analogy is with insulin activity: at times you want insulin to increase and spike to high levels, such as after a meal, but it's deleterious to health for insulin to be constantly elevated (hyperinsulinemia), as it leads to insulin resistance. With mTOR, spikes in its activity should be fine; chronic, low-level activation of mTOR is what leads to aging. That's my speculation and I don't want to speak for Dr. Green.

Update: A commenter below remarks: "As a patient of Dr. Green I appreciate the spread of information. I currently take 2 mgs of Rapamycin every 2 weeks and have noticed ZERO negative effects on my weight training and strength. BTW – I'm 63 and will be 64 in July." That's the sort of information we need but which is necessarily in short supply at this time. Likely we'll know a lot more about the interplay between rapamycin and muscle in 10 years time, when many more people will have been taking it. Meanwhile, the comment lends some support to my hypothesis that low, non-daily doses of rapamycin do not compromise muscle growth and/or resistance training.

A big thanks to Dr. Green for this interview.

PS: For some straight dope on anti-aging, see my book Stop the Clock.



PPS: Check out my Supplements Buying Guide for Men.

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