Risks and Benefits for Sirolimus in Aging Prevention

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Abstract

There is keen interest amongst the general population in preventing aging and age-related infirmities. Sirolimus is approved for preventing organ rejection in kidney transplant patients, has immune-modulating and growth-inhibitory properties, and is one of the therapies currently being used off-label for this purpose. There is a lack of formal guidance, such as a policy statement or position paper, on the appropriate dosing and administration of sirolimus for aging prevention. The American College of Clinical Pharmacology strongly recommends that clinicians prescribing sirolimus weigh the benefits and risks of sirolimus for off-label use in aging prevention, ensuring patients understand that such prescriptions lack any regulatory approval and rigorous supporting evidence. Health care providers are also encouraged to inform patients of the available clinical evidence and ongoing clinical trials in age-related conditions to build a stronger foundation of safety, efficacy, and optimal dosing for sirolimus in aging prevention.

Keywords

aging, longevity, mTOR, sirolimus

Background

Longevity, for some, means living a longer lifespan than expected, while for others, it is an increased or healthy lifespan (i.e., improved quality of life). Increased longevity necessitates not only successfully treating active illnesses, but also prevention for healthy individuals.

Aging may be defined as the processes that transform young individuals into aged ones, and these processes form the foundation for evaluating longevity as either a longer lifespan or increased health span as a possible disease state. Geroscience is a research paradigm based on understanding the genetic, molecular, and cellular mechanisms that make aging a major risk factor for and driver of common chronic conditions and diseases of older people.

Twelve hallmarks of aging have been recognized as key drivers in the aging process (examples include genomic instability, chronic inflammation, stem cell exhaustion, and dysregulated nutrient sensing), made complex by their interdependence with each other.[1] Hence, each of these hallmarks should be considered as a point of entry for future scientific investigation of aging and the development of new anti-aging medicines. Further, the study of longevity as the sole measure for aging can be confounded by specific pathologies. If early phenotyping markers could be identified even before the emergence of disease states or the beginning of hallmarks of aging, then it is theorized that early interventions might be used well in advance of these developing aging processes and thus, prevent future disease states.[2]

Whether aging should be classified as a disease is a matter of debate with no consensus. Leading scientific investigators describe aging as a "pathophysiological process," noting that its hallmarks include processes considered pathological.[1, 3] However, the medical community does not fully support this classification. For example, the World Health Organization recently considered classifying "Old Age" as a disease in the International Classification of Diseases 11th revision (ICD-11), only to retract it later. This decision was based on the view that aging is not a pathological process but rather a normal human attribute (i.e., aging-associated decline in intrinsic capacity). Further, the US FDA has not made any statements recognizing aging as a disease, let alone provided any guidance on the development of anti-aging medications. Therefore, given the interest in the general population in preventing aging and age-related infirmities and the lack of approved medications for this indication, a better understanding of how approved medications are currently being used off-label as anti-aging drugs, as well as information on dosing and administration

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for these drugs, is needed for the benefit of health care providers.

Drugs to Prevent/Ameliorate Aging

Senescence may be referred to as the aging process in which a cell stops dividing but does not die and can subsequently release proinflammatory substances. Metabolic alterations associated with the senescent state can be targeted using drugs referred to as senotherapeutics. Senotherapeutics can be broadly divided into two classes: senolytics, which selectively kill senescent cells (SnCs) or induce senolysis, and senomorphics, which attenuate the pathological senescence-associated secretory phenotype (SASPs) to cause senostasis.

Proof of senotherapeutic efficacy for the mitigation of age-related diseases has been supported by research utilizing mouse models of progeria and chronic disease and their rapid transition from discovery to clinical trials.[4] Senolytics have demonstrated the ability to alleviate many chronic ailments such as atherosclerosis and other cardiovascular dysfunctions, liver fibrosis, stem cell function, and others, along with a concomitant increase in healthspan. Examples of senolytics are dasatinib + quercetin, geldanamycin, digoxin, fenofibrate, azithromycin, etc., and senomorphics include sirolimus, metformin, ruxolitinib, atorvastatin, pravastatin, etc.[4]

One of the drugs most studied and utilized off-label for extending longevity is sirolimus (rapamycin, Rapammune) approved for prophylaxis of organ rejection in renal transplant patients and other indications.

Nonclinical Evidence for Sirolimus in Aging

At least five of the 12 hallmarks of aging are modulated by the mammalian target of rapamycin (mTOR), a protein that controls many cell functions, including cell growth, division, and survival. mTOR signaling is strongly implicated in the aging process of diverse organisms, such as yeast, worms, flies, and mammals. The mTOR kinases consist of two complexes, mTORC1 and mTORC2, which have overlapping and non-overlapping activity (i.e., phosphorylation of different substrates). The mTORC1 kinase is regulated by several nutrients, including amino acids, glucose, oxygen, and cholesterol, and it is this complex that has attracted interest with respect to aging.[5]

Numerous studies have shown that sirolimus, a potent and selective inhibitor of mTOR, could reduce cellular senescence and suppress SASP markers in a variety of mouse, rat, and human cell lines. In several invertebrate models, sirolimus increased the lifespan of yeast, worms, and flies.[4] The National Institute of Aging Interventions Testing Program (ITP) in 2009 found that administering sirolimus late in life extended both median and maximum lifespan of both male and female mice.[6] Similarly, many other vivo studies have demonstrated that sirolimus can alleviate age-related dysfunctions, delay tumor onset, decrease the rate of ageing, and increase lifespan in different mouse models.[4]

The ability of sirolimus to promote longevity is consistent with the idea that mTOR activity is an example of antagonistic pleiotropy, with high mTOR signaling being beneficial for development and reproduction but harmful during a post-reproductive old age.[5] Under such a model, the benefits of mTOR inhibition may arise less from specific benefits on processes such as translation and more from avoiding negative effects of hyperactive mTOR on processes such as cellular senescence. Indeed, sirolimus has been shown to inhibit the accumulation of senescent cells in mice as well as to suppress the senescence-associated secretory phenotype.[7]

Premature aging of the immune system has been shown to drive the aging of multiple other organ systems in mice.[8] These findings suggest that therapies that improve immune aging may have more systemic health benefits, possibly extending lifespan. mTOR inhibition has been shown to improve the function of the aging immune system in both mice and humans. Specifically, a short 6-week course of sirolimus has been shown to rejuvenate the function of hematopoietic stem cells, increase production of naive lymphocytes, and improve the response to influenza vaccination in old mice.[9] Of interest, sirolimus treatment extended lifespan in this study, even though it was only administered for 6 weeks when mice were already old (26 months).

Current Dosing Recommendations for Sirolimus in Approved Indications

Sirolimus Dosing for Approved Indications

The approved oral formulations of sirolimus include Rapamune Oral Solution and the sirolimus tablet formulation.[10] Both formulations are indicated for the prophylaxis of organ rejection in renal transplant patients. The approved doses of sirolimus for renal transplant patients start with a loading dose of 6 mg on day 1, followed by daily maintenance doses of 2 mg. The approved labeling also recommends adjusting doses to achieve sirolimus trough concentrations between 5 and 15 ng/mL. Further, it recommends reducing the maintenance dose in patients with hepatic impairment. The approved labeling also has a box warning for increased susceptibility to infection and possible development of lymphoma and other malignancies resulting from immunosuppression due to sirolimus.[11] In addition, the labeling recommends that only physicians experienced in immunosuppressive

therapy and management of renal transplant patients should use sirolimus for prophylaxis of organ rejection in patients receiving renal transplants.

The above approved dosing guidance for sirolimus, with recommendations of monitoring blood concentrations and the associated box warning, highlights the risks when prescribing these medications or using them for off-label purposes. Further, increased susceptibility to infection and possible development of malignancies, such as lymphoma and skin cancer, that may result from immunosuppression are the unintended safety concerns associated with off-label use of these medications.

Clinical Studies Evaluating Sirolimus to Support Off-Label Use as Antiaging Drug

Sirolimus has been assessed for the improvement of aging related functions in limited clinical studies. As it is not approved for aging or related indications, there is no recommended dose for use in otherwise healthy subjects.

A small pilot study conducted in healthy elderly (aged 70-93 years) volunteers assessed the safety and efficacy of sirolimus on several functional parameters relevant to aging.[12] The subjects were administered 1 mg Rapamune (sirolimus) tablets orally once daily for a duration of 8 weeks to 4 months, with resulting blood levels of 7.2 ± 2 ng/mL. The study demonstrated that with this relatively short duration of treatment, sirolimus was well tolerated. The investigators did not find any significant effect on the improvement of cognitive functions. They concluded that trials of longer duration and larger size with emphasis on specific parameters previously shown to be improved in animal models will be necessary to better understand the potential to modulate aging-related outcomes by mTOR inhibitors.

In another randomized placebo-controlled study of participants aged $\geq$40 years with signs of skin aging, 36 participants topically applied cream containing sirolimus (10 μM) to one hand and a matching placebo cream to their other hand every 24 to 48 h for 8 months.[13] A total of 17 participants completed the study, 13 participants had skin biopsies, and eight participants had sufficient biopsy material for analysis of p16 expression levels, the primary endpoint of the study. Sirolimus-treated subjects were observed to have a significant decrease in senescent cells as assessed by p16 expression, increased collagen VII protein expression, and clinical and histologically assessed improvements in skin appearance. Treated participants did not have detectable levels of sirolimus in their blood, and there were no treatment-related adverse events

In another study,[14] the authors collected data from 333 adults with a history of off-label use of sirolimus by survey. Similar data were also collected from 172 adults who had never used sirolimus. Among sirolimus users, 77.7% of men and 82.2% women reported taking sirolimus under the supervision of a physician. Among the reasons given for taking sirolimus, the most common answer was "healthy longevity/anti-aging," reported by 95% of users. Other responses included 62 individuals who reported taking sirolimus as a potential preventative for a higher risk of dementia as a result of carrying one or more APOE4 alleles, 27 individuals selected "cardiovascular disease," 12 individuals selected "cancer," and two individuals reported taking sirolimus for another indication. None of the study participants reported taking sirolimus for organ transplant rejection.

Participants reported a variety of different dosing strategies and dosing durations of sirolimus use. The most common dosing interval among sirolimus users was once weekly dosing, with 88.1% of male and 91.8% of female respondents reporting using this strategy. The second most common interval for dosing was 14 days. Only four participants reported using sirolimus daily. Other dosing intervals reported by users were between 5 and 17 days.

Similar to the case for dosing intervals, respondents reported a wide range of sirolimus doses taken. Among the individuals taking sirolimus weekly, 6 mg orally was the most common dose, with 101 out of 229 men and 25 out of 67 women reporting taking this dose. The minimum weekly dose for both men and women was 1 mg, and the maximum weekly dose was 20 and 14 mg, respectively. The median length of time on sirolimus among all survey respondents was 218 days. The most common dose and frequency (the mode) from the survey was 6 mg once a week,[14] and this lower dose/longer interval is theorized to be consistent with strategically achieving lower concentrations that would preferentially target mTORC1 relative to mTORC2; however, selective inhibition of mTORC1 has yet to be demonstrated in well-designed pharmacodynamic studies in patients.[5]

Regarding adverse events the authors reported that they found no evidence for significant increases in health risks, other than mouth sores, from off-label sirolimus use. A trend toward increased risk of bacterial and fungal infection associated with sirolimus use was noticed but did not reach statistical significance and appeared to be small in magnitude. They also noticed several positive effects with off-label sirolimus use, including significant reductions in eye pain, stomach pain, anxiety, and depression relative to non-users, in addition to a significant reduction in the severity of COVID-19 and risk of long-COVID among respondents. Overall. users expressed positive impressions of their experiences with sirolimus. However, the study has several limitations, which

include a lack of a double-blind, randomized controlled design, the self-reported nature of the data, the possibility that the population of sirolimus users is self-selected against people who started taking sirolimus and stopped because of negative experiences, and the possibility that individuals taking sirolimus off-label may be more likely to practice healthy lifestyle habits.

Clinical Prescribing Perspective of SIROLIMUS

Clinicians adhering to FDA-approved indications prescribe sirolimus to renal transplant patients or those with lymphangioleiomyomatosis as indicated in the approved label. However, the mentioned earlier prescriptions for aging prevention are off-label use of this drug. For perspective, approximately 11% of prescriptions in the United States are off-label [15]. While the exact percentage of off-label prescriptions of sirolimus is not available, severe adverse events have been reported on the off-label use of sirolimus.[16]

When prescribing off-label sirolimus for aging prevention, it is important to keep in mind the risk-benefit for each patient. Multiple clinical trials of sirolimus in aging are ongoing, assessing both safety and efficacy, including disease-specific endpoints such as glucose tolerance and insulin sensitivity, muscle regeneration, Alzheimer's dementia, and cognitive health, all of which will further inform risk-benefit clinician-patient discussions.[17] Patients can be made aware of these trials to add to the knowledge from systematically studying the effect of sirolimus on aging indicators.

Physicians and patients considering off-label sirolimus use should consider when to adjust, stop, or avoid treatment, particularly in patients with infections, malignancies, or inflammatory conditions requiring immunosuppression. Other factors that need to be considered include the potential for drug interactions with other medications and interactions with food.[10] Sirolimus is a CYP3A4 and p-glycoprotein substrate and drugs that are inhibitors or inducers of these which include several commonly prescribed drugs such as antivirals, antimicrobials, nonsteroidal anti-inflammatories, benzodiazepines, calcium channel blockers, antiepileptics and proton pump inhibitors can result in changes in sirolimus blood levels, warranting frequent monitoring, and dose adjustments.

Also, clinicians must use caution in the language chosen to convey certainty around benefit claims when prescribing sirolimus for aging prevention to avoid misinterpretation by patients that benefits exceed current rigorous clinical evidence.

A final consideration for clinicians is when to begin prescribing sirolimus for aging prevention to achieve its optimal impact, assuming such a time frame can be determined. This information is ideally determined by data from controlled clinical trials.

Discussion

While the safety profile of sirolimus doses ($\leq$6mg) in humans appears promising, a much better understanding is needed of the specific dose and duration of sirolimus that both maximize efficacy and minimize risk. Given the absence of regulatory guidance, regulatory frameworks need to be defined for aging-related indications.

Doses of sirolimus (1-10 mg per week) on a once-daily or once-weekly dosing schedule have been used in limited controlled clinical studies. The regimen of 6mg once a week was the most common dose and frequency.[14] However, to the best of the authors' knowledge and literature search in this area, none of the studies demonstrated a direct impact on the aging or senescence-related primary endpoints, which is not unexpected as defining and conducting a study with aging-related primary endpoint can be challenging. It appears that currently, off-label use of sirolimus in aging involves weekly doses ($<$10 mg) where the dose and dosing frequency are essentially individually determined based on tolerance for the medication.

Clinicians prescribing sirolimus must weigh the risks and benefits, particularly for off-label use in aging prevention, ensuring patients understand that such prescriptions lack FDA approval and rigorous supporting evidence. Physicians should encourage patients to participate in clinical trials involving age-related conditions to build a stronger foundation of safety, efficacy, and optimal dosing for sirolimus in aging prevention.

Effective clinician-patient discussions about off-label sirolimus use should incorporate considerations of patient-specific factors, including comorbidities, potential drug interactions, and evidence-based risk-benefit analysis. As more data emerges from ongoing research, these discussions will become increasingly informed, allowing for better alignment of treatment goals with clinical evidence.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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