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COVID-19 disproportionately affects older people, with likelihood of severe complications and death mirroring that of other age-associated diseases. Inhibition of the mechanistic target of rapamycin complex 1 (mTORC1) has been shown to delay or reverse many age-related phenotypes, including declining immune function. Rapamycin (sirolimus) and rapamycin derivatives are US Food and Drug Administration-approved inhibitors of mTORC1 with broad clinical utility and well established dosing and safety profiles. Based on preclinical and clinical evidence, a strong case can be made for immediate large-scale clinical trials to assess whether rapamycin and other mTORC1 inhibitors can prevent COVID-19 infection in these populations and also to determine whether these drugs can improve outcomes in patients with severe COVID-19.

Introduction

The first case of infection caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, in December, 2019. On March 11, 2020, WHO declared COVID-19 a global pandemic. Since then, COVID-19 has affected the lives of billions of people; as of December, 2020, it is estimated that nearly 65 million people have been infected with and 1·8 million have died of COVID-19. After the rate of new infections and deaths plateaued after the first wave, the infection incidence is currently rapidly increasing again, as are concerns regarding the ongoing second wave and potential further waves, and the long-term effects following infection and recovery. Globally, we are observing geographical redistribution of hotspots and are faced with the distinct possibility that outbreaks could reoccur not only in the months, but perhaps years ahead.

Similar to other viral infections, such as influenza, older people (eg, ≥65 years) are at a substantially increased risk of suffering adverse outcomes from COVID-19.1 Although it remains too early to know the extent to which age affects the risk of initial infection, it is clear that age is by far the greatest risk factor for severe COVID-19 complications and death. Data from the US Centers for Disease Control and Prevention reveal that the risk of dying from COVID-19 increases approximately 10-fold for every 20 years of age.2 This association between age and risk of COVID-19 mortality is comparable with the relationship between age and risk of death from Alzheimer’s disease.3

We have postulated that the relationship between chronological age and COVID-19 mortality is driven primarily by the biological mechanisms of ageing; a concept which has recently become more widely appreciated among clinicians and researchers.4 At the cellular and molecular levels, these mechanisms have been described as the hallmarks5 or pillars6 of ageing. Previous research has revealed that these hallmarks can be directly linked to the age-associated loss of immune function concomitant with increases in systemic inflammation (also referred to as inflammaging).7 Inflammaging can be seen in the form of aberrant activation of innate immune mechanisms, such as elevation of pro-inflammatory cytokines and increased numbers of natural killer cells,8 with such activation exacerbating the increased risk of viral and bacterial infections that are associated with age. Impairment of immune function could also contribute to additional age-associated problems, including increased prevalence of autoimmune disorders and increased risk for numerous types of cancer due to impaired immune surveillance.8,9

The immune system loses efficacy with age.9 Immunosenescence affects both innate and acquired immunity and greatly reduces the production of naive T-cells and B-cells in the thymus and bone marrow. Consequently, decreased antibody production leads to fewer T cell and B cell interactions, and a reduced release of thyroid hormones, thus leading to decreased natural killer cell activity and a functional decline in the body’s ability to mount an immune response.10 Older people are known to have a chronic low-threshold proinflammatory status along with elevated plasma markers (eg, interleukin-6, tumour necrosis factor-α, and C-reactive protein) in the absence of clinical symptoms.8 On a cellular level, this translates to enhanced inflammatory activity, especially in monocytes and macrophages (ie, the innate immune system) that work to reciprocally enforce the ongoing inflammaging processes.9

The collective outcome is a compromised immune response and an increased incidence of inflammatory comorbidities—eg, cancers and age-related neurodegeneration, which further weaken the immune system.8,10 The innate immune system, which is primarily involved in the response to new infections, is also compromised due to a reduction in clonal diversity.11 This reciprocal relationship between inflammaging and immunosenescence is believed to underlie the adaptive processes, which exacerbates the severity of symptoms in older individuals who tend to exhibit an enhanced susceptibility towards infections along with a diminished response to vaccines.12–14 Therefore, we and others propose that novel and effective strategies for combating COVID-19 can be developed by directly targeting the hallmarks of ageing to prevent or diminish inflammaging and immunosenescence.7,8,12
mTOR inhibition increases lifespan and health in preclinical research

Studies investigating the mechanistic target of rapamycin (mTOR) pathway have shown that immunosenescence can be reversed by targeting biological ageing. The mTOR protein is a nutrient-responsive and stress-responsive kinase that functions as a conserved regulator of ageing in eukaryotes. Activation of mTOR promotes development and growth, whereas genetic inhibition of mTOR increases lifespan in yeast, nematodes, fruit flies, and mice. The mTOR kinase acts in two distinct protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). In the context of biological ageing, inhibition of mTORC1 is consistently associated with increased lifespan, whereas inhibition of mTORC2 is associated with reduced lifespan, at least in mice. mTORC1 regulates several key homoeostatic processes including autophagy, mRNA translation, and metabolism, each of which affects the hallmarks of ageing and, therefore, the lifespan of different model organisms.

The macrolide antibiotic rapamycin (sirolimus) is an allosteric inhibitor of mTORC1 that acts by binding to the FK506 binding protein (FKBP12). Similar to genetic inhibition of mTORC1, rapamycin has been shown to increase lifespan in yeast, nematode worms, fruit flies, and mice. The effects of rapamycin on lifespan have been robust in mice, with lifespan extension being reported in multiple strain backgrounds across a broad dose range, involving both oral delivery and intraperitoneal injection. Lifespan extension is comparable when treatment is initiated at young age, in mid-life, or transiently in late life. Intermittent treatment with rapamycin in late life has also been shown to be effective at extending lifespan. Importantly, the effects of rapamycin extend beyond increasing lifespan in mice, with evidence of reduction in hallmarks of ageing. These effects include fewer age-related cancers, protection against cognitive decline, improved cardiovascular function, restoration of immune function, and improved renal function, oral health, intestinal function and reduced gut dysbiosis, and preserved ovarian function.

Other pharmacological inhibitors of mTOR have been described but there is relatively little data on their effects on lifespan or health during ageing. In general, existing mTOR inhibitors can be classified into three categories: rapamycin derivatives (rapalogs), other mTORC1-specific inhibitors not structurally related to rapamycin, and ATP-competitive inhibitors of mTOR. Rapalogs and other mTORC1-specific inhibitors are generally predicted to function similarly to rapamycin in enhancing lifespan and improving age-related phenotypes; however, only everolimus (known as RAD001) has been studied in this context. The evidence supporting geroprotective effects from everolimus include improved muscle function during ageing in rats and improved immune function in healthy older people. ATP-competitive inhibitors, which inhibit mTORC1 and mTORC2, usually have off-target effects on other kinases. Examples of ATP-competitive inhibitors of mTOR include Torin 1, Torin 2, and the PI3K/mTOR dual kinase inhibitors such as dactolisib (known as BEZ235 or RTB101). To our knowledge, there are scarce data supporting the positive effects of ATP-competitive mTOR inhibitors on lifespan in any research done in animals and only rapamycin has been shown to increase lifespan in mice.

Inhibition of mTOR reverses age-related decline in immune function

Although rapamycin and rapalogs have usually been considered immunosuppressives, multiple studies have shown that rapalog monotherapy is sufficient to reverse age-related declines in immune function in mice and people. One of the first studies to show the effectiveness of rapalogs was done using research done in mice that investigated age-related immune senescence. In that study, aged mice (aged 22–24 months) were treated with either rapamycin or a vehicle control for a period of 6 weeks. After a 2-week washout period, mice in each group were immunised against H1N1 influenza. 2 weeks later, both groups were challenged with live H1N1 and their survival was quantified. When compared with young immunised mice (aged 2 months), the aged mice that did not receive rapamycin exhibited a substantial reduction in response to the vaccine, with approximately two-thirds of the mice failing to mount an immune response and dying within 10 days of H1N1 challenge. By contrast, aged mice that received rapamycin exhibited improved immune function, with all of the rapamycin-treated mice responding to the vaccine and surviving the subsequent H1N1 challenge past the endpoint of the experiment. This functional rejuvenation was associated with a decrease in senescence markers in haematopoietic stem cells along with improved stem-cell function, although the precise mechanism of action remains to be established.

This preclinical work spurred efforts to assess whether similar outcomes would be seen in a clinical setting. Two phase 2 clinical trials have been completed in which older healthy adults were treated with everolimus alone or everolimus combined with RTB10157 for 6 weeks. Both studies were randomised, placebo-controlled and found that patients who were given the rapalog showed improved responses to influenza vaccine when compared with those who received the placebo only. In the study using a combined treatment, patients who received everolimus plus RTB101 also had fewer infections over the following year, suggesting that the immune-boosting effect might extend beyond the initial vaccine response. Enhanced autophagy because of mTOR inhibition along with increased expression of anti-viral proteins have been proposed as potential mechanisms of action for the observed immune-boosting effects in people. However, a subsequent phase 3 clinical trial using RTB101 alone did not meet its endpoint.
The observation that immune function can be improved over a period of several weeks to months following a single 6-week interval of mTORC1 inhibition has important clinical implications. Influenza alone is estimated to result in 30,000 to 50,000 deaths annually, with older individuals at highest risk. Improving vaccine response among this susceptible population could substantially enhance preventive measures and reduce severe clinical outcomes. A transient treatment regimen is also likely to be more easily adopted across large cohorts and have substantially fewer adverse effects compared with chronic high-dose regimens adopted by organ transplant patients. Indeed, no clinically significant adverse events were noted in either of the phase 2 mTOR inhibitor trials, and there is growing evidence that low-dose rapalog monotherapy has minimal side-effects in healthy older adults. These findings are further supported by the absence of observed side-effects in non-human primate marmosets and in older companion dogs treated with lower doses of rapamycin.

A restoration of immune function in older adults is likely to have benefits that extend beyond simply boosting the response to an influenza vaccine. Before COVID-19, respiratory infections were estimated to account for more than 1 million deaths in adults older than 70 years and more than 2 million deaths in people of all ages annually worldwide, numbers that were much higher in 2020. Additionally, it is expected that enhanced immune function would lead to reduced rates of age-associated cancers, as immune surveillance is known to be a crucial anti-cancer mechanism that is impaired by the aging process. Reversion of age-related changes in the microbiome could also be expected following mTOR inhibition, as the immune system plays an important role in maintaining a healthy microbiome. Rapamycin has been found to reduce age-related cancers and modify the aged microbiome in mice, although it remains to be established whether these effects are mediated by the immune system.

### Evaluating the feasibility of rapamycin for COVID-19 prevention

The most important consideration for any clinical intervention is to evaluate the potential benefit against the potential risk. This evaluation is always challenging to quantify but is even more difficult for a preventive treatment that is given to individuals who are not currently sick. As discussed, the potential benefits of preventing immunosenescence in older people are quite large and include reductions in morbidity and mortality from infectious disease and cancer. Regarding COVID-19, extrapolation from preclinical studies suggests that the immune restorative properties of rapamycin might be expected to reduce COVID-19 deaths substantially in the absence of a vaccine and possibly by an even greater amount once a vaccine is widely available.

Because there are abundant clinical data on rapamycin use, we can also predict the potential risks. Rapamycin and other rapalogues (ie, everolimus, temsirolimus) have been widely used to prevent organ transplant rejection but are also approved for use in lymphangioleiomyomatosis, coronary stenting, and particular types of cancer (eg, hormone receptor positive breast cancer or neuroendocrine tumours). Use of high-dose rapamycin (>15–25mg/kg) by organ transplant patients is associated with numerous side-effects including generalised pain (≥30% occurrence, leading to a 5% treatment discontinuation rate), headache, fever, hypertension, nausea, abdominal pain, constipation, diarrhoea, urinary tract infection, peripheral oedema, anaemia, arthralgia, thrombocytopenia, hypercholesterolaemia, hypertiglyceridaemia, and increased creatinine. Side-effects are mostly reversible and represent a worst-case scenario, as these patients are severely ill and taking high doses of the drug along with other treatments.

### Table: Clinical trials of mTOR inhibitors and treatment of COVID-19

| Study | Recruitment status | Estimated enrolment | Study start date | Intervention group | Control group |
|-------|-------------------|---------------------|------------------|--------------------|---------------|
| Efficacy and safety of sirolimus in COVID-19 infection (NCT04461340) | Recruiting | 40 | July 25, 2020 | 20 patients will receive sirolimus (oral dose of 6 mg on day 1 followed by 2 mg daily for 9 days) plus national standard of care therapy against COVID-19 | Placebo plus standard medical care |
| Sirolimus treatment in hospitalised patients with COVID-19 pneumonia (NCT043416/75) | Recruiting | 30 | April 24, 2020 | Sirolimus 6 mg on day 1 followed by 2 mg daily for the next 13 days or until hospital discharge, whichever happens sooner | Placebo plus standard medical care |
| Sirolimus in COVID-19 phase 1 (NCT04371640) | Recruiting | 40 | July 6, 2020 | Sirolimus 10 mg on day 1 followed by 5 mg on days 2-7 plus standard medical care | Placebo plus standard medical care |
| Hydroxychloroquine in combination with azithromycin or sirolimus for treating patients with COVID-19 (NCT04374903) | Not yet recruiting | 58 | May 1, 2020 | Participants will receive 600 mg hydroxychloroquine orally for 10 days and 250 mg azithromycin orally daily for 10 days, or sirolimus 4 mg orally for 1 day then 2 mg orally daily for 9 days | Placebo plus standard medical care |
| Phase 3 study to determine if RTB101 reduces the severity of COVID-19 in older adults residing in nursing homes (NCT04460327) | Recruiting | 550 | July 11, 2020 | 10 mg daily RTB101 mTORC1 inhibitor (once daily for 4 weeks) | Placebo plus standard medical care |

These studies were found using a search for COVID-19-related clinical trials on ClinicalTrials.gov on Oct 23, 2020. mTOR=mechanistic target of rapamycin, mTORC1=mTOR complex 1.
Panel: Initial recommendations for a clinical trial assessing the effects of rapamycin on COVID-19 outcomes and vaccine response

**General design**
An ideal design is a double masked and placebo-controlled randomised controlled trial.

**Patient population**
We suggest enrolling older adults (eg, ≥60 years) who are predicted to have a biological age that is at least 5 years older than their chronological age.

**Cohort sizes**
Would be determined based on predicted infection rate and progression to severe outcomes. Several thousand people per study group would probably be needed.

**Dose**
5–10 mg rapamycin orally provided once per week.

**Duration**
6–10 weeks treatment with 8–10 months follow-up.

**Exclusion criteria**
Previous COVID-19 infection, immune compromised, or active infection.

**Endpoints**
Rates of COVID-19 infection, severity of outcomes (eg, hospitalisation, death), vaccine response (if available).

medications. Risk of serious complications, even from acute overdose with rapamycin, is extremely low. For this reason, we believe that short-term treatment (up to a few months) with low doses (eg, a range of 5–10 mg weekly) of rapamycin will have minimal adverse events and that the risk–reward ratio strongly favours the potential beneficial effects from treatment.

To our knowledge, there are no active or planned clinical trials of rapamycin or rapalogs as a preventive treatment for COVID-19. As of November, 2020, there were 214 incomplete clinical trials registered on ClinicalTrials.gov, identified using the search term “rapamycin” or “sirolimus”; five of these trials are related to COVID-19 (table). In each of the existing or planned trials, rapamycin is being tested as a treatment in hospitalised patients with confirmed COVID-19, with primary endpoints such as the change in SARS-CoV-2 viral burden and time to clinical recovery. Thus, the rationale for potential efficacy in these trials, based on the ability of rapamycin to prevent the cytokine storm seen in patients with severe COVID-19 or its potential direct anti-viral effects, is quite different from the effects of rapamycin on biological ageing. The biopharmaceutical company restORbio (Boston, MA, USA) initiated a small clinical trial of RTB101 in nursing home residents, to determine whether COVID-19 severity is affected by the dose of rapamycin, duration of treatment, demographic features of the patients enrolled in the study, specific endpoints to be evaluated, the duration of follow-up, and necessary cohort sizes to reach statistical power (panel, appendix). Although the simplest study design would include only placebo and rapamycin treatment groups, a multi-arm design that is worth considering, would provide ongoing protection against other infections that preferentially affect older people.

The details of a well designed randomised clinical trial would need to be carefully considered, including the dose of rapamycin, duration of treatment, demographic features of the patients enrolled in the study, specific endpoints to be evaluated, the duration of follow-up, and necessary cohort sizes to reach statistical power (panel, appendix). Although the simplest study design would include only placebo and rapamycin treatment groups, a multi-arm design that is worth considering, would provide ongoing protection against other infections that preferentially affect older people.

One innovative feature that we suggest should be incorporated into a trial is the consideration of predicted biological age as an enrolment criterion. Although there is supportive data from a phase 2 study suggesting that everolimus plus RTB101 can improve immune function in older people, RTB101 acts by a different biochemical mechanism from rapamycin and has not yet been shown preclinically to have effects on biological ageing. Thus, although we are hopeful that these ongoing clinical trials will prove successful, none of them address the possibility that rapamycin will rejuvenate immune function in older people and afford protection against COVID-19 to the most susceptible individuals.

We strongly advocate for a large-scale clinical trial in at-risk populations to test for prevention of COVID-19 by rapamycin. The rationale for such a trial is provided by the observed ability of rapamycin and rapalogs to reverse age-related declines in immune function in preclinical models and in people. Older patients have substantially worse clinical outcomes following COVID-19 infection, and preventive treatment with rapamycin is predicted to reduce rates of infection and improve clinical outcomes by reducing the number and severity of complications in biologically aged patients. Based on research done in mice, we hypothesise that rapamycin will restore immune function corresponding to approximately 20 years of biological age, thereby reducing severe outcomes and death from COVID-19 by approximately 4–10-times. Furthermore, enhanced immune function following rapamycin treatment is expected to improve the response to the COVID-19 vaccines and provide ongoing protection against other infections that preferentially affect older people.

The preclinical evidence that metformin can positively affect the aged immune system is less robust than that for rapamycin; however, there is accumulating evidence that people with diabetes taking metformin are at reduced risk of severe outcomes or death from COVID-19 compared with people with diabetes not taking metformin. Furthermore, metformin combined with rapamycin in mice is thought to improve metabolic function and slightly further increase lifespan, relative to rapamycin alone. One innovative feature that we suggest should be incorporated into a trial is the consideration of predicted biological age as an enrolment criterion. Enrolment based on chronological age is common in clinical
studies, similar to the design of the rapalog trials that investigated influenza vaccine response.\textsuperscript{6,7} However, we propose that it could be useful to consider newly developed measures of predicted biological age for geroprotective clinical trials. Such biological age predictors could include estimates of epigenetic age using commonly applied epigenetic clocks\textsuperscript{8,9} and so-called deep ageing clocks,\textsuperscript{9} based on signatures derived from blood biochemistry, imaging, transcriptomics, and other types of available data. Patients whose biological age exceeds their chronological age by a chosen threshold (e.g., 5 years) could be enrolled, thus targeting individuals at the highest risk for negative outcomes and death and who are predicted to receive the greatest benefit from a geroprotective intervention such as rapamycin. Although we recognise that the mechanisms and predictive power of current biological age estimators have yet to be clinically validated and could present unique challenges from a regulatory perspective, there is growing consensus among researchers investigating artificial intelligence and ageing that these tools can provide valuable insights into underlying physiological states that affect risk for age-related diseases and for all-cause mortality. However, they could be used as auxiliary markers until clinical validation in COVID-19 has been achieved.

A final consideration might be whether, even once shown to be efficacious, widespread use of a geroprotective intervention is economically feasible or justified, given the strain on many national health-care systems. Because there is more than one COVID-19 vaccine available, there is a danger that the incentive to continue to develop novel preventive therapies will decrease. However, influenza deaths still number in the hundreds of thousands each year even with effective vaccines, and those most susceptible to severe cases of both COVID-19 and influenza are also the least likely to mount an effective vaccine response. Thus, from the perspective of cost in terms of human lives, justification for this type of approach is obvious. It is also well established that the total economic benefit from a successful geroprotective therapy far outweighs the cost of development and implementation. Work from Goldman\textsuperscript{10} and Olshansky\textsuperscript{2} done before the COVID-19 pandemic has estimated that the total economic benefit from such an intervention will exceed US$7 trillion over the next 3–4 decades. The total economic value of an effective geroprotective strategy is likely to be substantially greater today than before the pandemic.

Conclusion
SARS-CoV-2 disproportionately affects older people and people with comorbidities, with likelihood of severe complications and death mirroring that of other age-associated diseases. Inhibition of mTOR has been shown to delay or reverse many age-related phenotypes, including declining immune function. There is an urgent need for a precision medicine trial using a functional metric of ageing that investigates individuals assessed by biological age, who can then be further stratified into groups of those individuals who achieve optimal outcomes and benefit from the treatment. Rapamycin and rapamycin derivatives (rapalogs) are FDA-approved inhibitors of mTOR with broad clinical utility and well established dosing and safety profiles. Based on pre-clinical and clinical evidence, a strong case can be made for immediate large-scale clinical trials to assess whether rapamycin and other mTOR inhibitors can enhance resilience towards communicable and non-communicable diseases, prevent COVID-19 infection in those most at risk, and improve outcomes in patients with COVID-19.

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