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Clinical trials of mTOR inhibitors to boost immunity to viral infection in older adults

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Respiratory tract infections (RTIs), mainly caused by viruses, are a major cause of morbidity and mortality in older people (aged >65 years).[1] During the COVID-19 pandemic, increasing age has proved to be the major risk factor for serious illness and death from infection with SARS-CoV-2. The increased susceptibility of older people to viral RTIs is at least partly driven by age-related decline in immune function, characterised by dysregulation of both innate and adaptive immune responses. In particular, attenuated type I interferon (IFN) response, the first line of defence against viruses, might play a major role. In support of this hypothesis, neutralising autoantibodies against type I IFN and enrichment in loss-of-function mutations in IFN-related genes were reported in patients with life-threatening COVID-19 pneumonia.[2,3]

A characteristic feature of the ageing process is overactivity of the mechanistic target of rapamycin (mTOR) signalling pathway. Inhibition of this this pathway can increase lifespan and health during ageing in pre-clinical models and also reduces the incidence of RTIs in mice[4] and augments the type I IFN response.[5] Importantly, in a previous clinical trial, mTOR inhibitors were shown to be effective in enhancing the immune response of adults aged at least 65 years to influenza vaccine.[6] Furthermore, in a phase 2a clinical trial, an oral mTOR inhibitor (RTB101) increased IFN-induced antiviral gene expression and decreased the incidence of respiratory tract infections (RTIs) in adults aged at least 65 years.[7]

Motivated by their promising previous findings, Joan Mannick and colleagues[8] did phase 2b and phase 3 clinical trials, reported in *The Lancet Healthy Longevity*. Both trials were multicentre, randomised, double-blinded, and placebo-controlled, and patients were treated in the winter cold and influenza season for 16 weeks. The phase 2b trial enrolled 652 participants with an increased risk of RTI—ie aged 65–85 years, with an underlying condition such as asthma or chronic obstructive pulmonary disease (COPD), and current smokers. Patients were treated with RTB101 alone, or in combination with another mTOR inhibitor everolimus, or with placebo. Once daily treatment with 10 mg RTB101 alone significantly reduced the overall proportion of patients with one or more laboratory-confirmed RTIs, confirming the previous phase 2a trial results (34 [19%] of 176 patients *vs* 50 [28%] of 180; odds ratio [OR] 0·601 [90% CI 0·391–0·922]; p=0·02). The treatment had no effect in current smokers or people with COPD and had the greatest effect in patients older than 85 years or older than 65 years with asthma. Of note, RTB101 reduced the proportion of patients with laboratory-confirmed RTI with severe symptoms by 50% compared with in the placebo group (17 [9%] of 180 patients in the placebo group *vs* eight [5%] of 176 in the RTB101 treatment group; OR 0·44 [90% CI 0·21–0·92]; p=0·034).

The phase 3 trial enrolled 1024 individuals aged at least 65 years, who did not have COPD and who were not current smokers, and compared daily treatment with 10 mg RTB101 with placebo. The US Food and Drug Administration requested a change in primary endpoint between the phase 2b and phase 3 trials because of concerns that laboratory confirmation of an infection was not relevant to how patients feel and function. The primary endpoint was hence altered to the proportion of patients with at least one symptom consistent with an RTI. Compared with the phase 2b trial, the phase 3 trial was thus done in patients who were at lower overall risk of RTIs and with a primary endpoint that was less clearly linked to underlying immune function. Perhaps for these reasons, the authors found no significant decrease in RTIs as defined by the primary endpoint.

In both the phase 2a and phase 3 trials, daily treatment with RTB101 increased expression of IFN-responsive genes in whole blood compared with placebo. The authors made the interesting suggestion that enhancing IFN-induced gene expression might be particularly effective against RTIs caused by coronaviruses and influenza viruses, which have been reported to suppress the host IFN response.

The COVID-19 pandemic has highlighted the necessity of enhancing the immune function in older people. Although the phase 3 study did not meet its primary endpoint, important questions remain. Further work is needed to investigate whether mTOR inhibition

prevents RTIs in specific sub-populations or if inhibition is more effective against specific types of viruses. These findings also open new questions about the precise mechanism and pathways by which mTOR inhibition engages the type I IFN response and whether mTOR inhibitors can induce additional enhancements to an aging immune system. RTB101 might also ameliorate other effects of ageing in humans, since in mice mTOR inhibition can attenuate age-related cognitive decline[9] and cardiovascular complications.[10] Mannick and colleagues' study establishes the important principle that it is possible to safely target an aspect of the aging processes to enhance aspects of immune function and will serve as a cornerstone for future studies focusing on enhancing function in the ageing population.

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