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LETTER TO THE EDITOR

Jakub Cecot[1], Konrad Zarzecki[2], Miłosz Mandryk[2]

[1]J. Mikulicz-Radecki University Clinical Hospital, Wroclaw, Poland
[2]4th Clinical Military Hospital, Wroclaw, Poland

Senolytic effect of canagliflozin, a new possible line of treatment for age-related diseases

Dear Editor,

In this letter we would like to highlight some recently discovered positive properties and possible effects of canagliflozin in the treatment of age-related diseases. Canagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor primarily used as an oral treatment for type 2 diabetes (T2D). Its mechanism for reducing blood glucose levels is insulin-independent and involves reduction of renal reabsorption of glucose, mainly in the proximal tubule, resulting in increased secretion of glucose in the urine. In multiple clinical trials, it has proven its effectiveness in improvement of glycemic control in adults with T2D, especially those with higher cardiovascular risk and at a more senior age. Diabetes management is not the only application in which canagliflozin has shown its viability, it has been found that it improves cardiovascular and renal outcomes in patients with T2D [1, 2], promotes weight reduction and improves blood pressure [3, 4]. It is generally safe and well-tolerated, with a low risk of hypoglycemia and the most common adverse effects being genitourinary tract infections and increased urination.

A recently published article by Katsuumi et al. [5] shows promising results on the effect of canagliflozin on the removal of senescent cells from the body. Senescence is a permanent state of cell cycle arrest accelerated by DNA damage resulting from aging or metabolic stress. It has been recognized to contribute to the aging phenotype and aging-associated diseases such as atherosclerosis, cancer, hypertension and T2D [6]. In the aforementioned study using a mice model, it has been found that inhibition of SGLT2 receptors plays a major role in enhancing senescent cells clearance. An experiment was conducted, where mice were fed a high-fat diet, followed by receiving short- and long-term canagliflozin treatment. Activity of senescence-associated-beta-galactosidase (SA-β-gal) was measured and a decrease in activity was revealed. The result of this treatment was also a notable reduction in adipose tissue inflammation and improvement of metabolic parameters, which signalized canagliflozin potential in mitigating possible age-related diseases. For enriched understanding of its acting mechanisms, metabolomic analyses were conducted, showing elevated levels of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), which acts as an activator of AMP-activated protein kinase (AMPK). Activation of AMPK lead to a significant reduction in senescent cells and their senescence-associated secretory phenotype in tissues. Exogenous AMPK inhibition reversed these effects, confirming the role of this pathway in canagliflozin's senolytic action. Canagliflozin also plays a role in reduction of PD-L1 ligand expression on senescent cell surface through AMPK activation, which boosts immunosurveillance and senescent cells clearance. Another finding was a fact that canagliflozin treatment leads to beneficial senescence-associated changes in the aorta,

Corresponding author:

Jakub Cecot MD, J. Mikulicz-Radecki University Clinical Hospital, Borowska 213 St., 50–556 Wrocław, Poland, e-mail: jakubcecot1@gmail.com, phone: +48 48 575251098

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such as decreased SA-β-gal, decreased plaque area and reduced inflammatory markers expression [5]. This suggests the potential for discovering new lines of treatment for many age-related diseases.

The previously mentioned findings indicate promising results regarding canagliflozin use in treatment of age-related and metabolic diseases; however, further research and clinical trials are necessary to establish relevant schemes and guidelines for these emerging therapeutic solutions.

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