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LETTER TO THE EDITOR

Statin Therapy and Survival among Women with Ovarian Cancer: how much of it Is True?

Raffaella Mormile [1]

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Statin use following a diagnosis with ovarian cancer has been reported to be connected with a lower risk of cancer death [1, 2]. Statin use has been observed to exert a protective effect on ovarian cancer-specific and all-cause mortality [2]. Ovarian cancer patients who use statins after diagnosis have been found to have an important reduction in overall mortality in comparison to statin nonusers [2]. Statins represent the most commonly utilized drugs to lower serum low-density lipoprotein cholesterol levels [2]. Statins have been demonstrated to reduce both cholesterol and inflammation [3, 4]. Statin use has been discovered to have anti-inflammatory capacities, in addition to its cholesterol-lowering effect [3]. It has been suggested that statins potently decrease the cytokine-mediated interleukin-6 (IL-6) release [3]. Simvastatin, atorvastatin, fluvastatin or pravastatin have been revealed to significantly reduce IL-6 production in a dose-dependent manner when compared with the control group [3, 4]. Statins have also been found to dampen inflammation through induction of an anti-inflammatory form of the pro-inflammatory interleukin-1β (IL-1β) [5]. IL-1β is produced as a non-active precursor which is processed into an active form [5]. IL-1β has been demonstrated to promote ovarian tumorigenesis as a communication factor in order to generate a pro-tumorigenic inflammatory microenvironment [6, 7]. It has been verified that processing of pro-IL-1β upon statin-stimulation leads to an intermediate form of IL-1β which is not biologically active itself, but interferes with mature IL-1β-IL-RI signaling [5]. Interestingly, it has been proved that IL-6 may be induced in response to IL-1β [6]. Epithelial ovarian cancer represents the most fatal gynecologic malignancy worldwide [8, 9]. Most ovarian cancer patients become resistant to chemotherapy despite the initial response to therapeutic agents are promising [8]. Inflammation has been recognized to play many roles in ovarian cancer tumor growth with IL-6 having been recognized as a crucial immuno-regulatory cytokine [8]. IL-6 has been stated to directly elicit enhanced invasion of ovarian cancer cells through basement membrane degradation, stimulate promotion of cell cycle, increase resistance to chemotherapy, and cause epithelial-to-mesenchymal transition [8]. IL-6 has been detected to trigger signaling pathways leading to tumor proliferation [8]. IL-6-induced JAK/STAT activation has been found to result in constitutive activation of STAT3 which appears to relate to enhanced tumor cell growth and resistance to chemotherapy [8]. Concordantly, the expression level of IL-6 and IL-6 receptor (IL-6R) has been documented to be higher in therapy resistant ovarian cancer cells in comparison to sensitive ones [9]. STAT3 tyrosine phosphorylation has been detected to play a critical role both in IL-1β and IL-6 production in response to inflammation [10]. Taken together, I hypothesize that statin therapy may improve survival among women with ovarian cancer by its inhibitory interactions with IL-6, IL-1β and STAT3 signaling pathway. By acting on IL-6, IL-1β and STAT3 signaling pathway, statins appear to specifically affect some of the main molecular pathways which are involved in the pathogenesis and biological features of ovarian cancer. In this light, I assume that there is a rational belief in promoting randomized controlled trials for statin use among possible therapeutic options in the management of ovarian cancer in terms of drug repositioning approach to overcome chemoresistance.

✉ Raffaella Mormile
raffaellamormile@alice.it

[1] Division of Pediatrics and Neonatology, Moscati Hospital, Via A. Gramsci, 81031 Aversa, Italy

Compliance with Ethical Standards

Conflict of Interest The author declares no potential conflicts of interest.

References

1. Harding BN, Delaney JA, Urban RR, Weiss NS (2019) Use of statin medications following diagnosis in relation to survival among women with ovarian cancer. Cancer Epidemiol Biomark Prev 28: 1127–1133
2. Couttenier A, Lacroix O, Vaes E, Cardwell CR, De Schutter H, Robert A (2017) Statin use is associated with improved survival in ovarian cancer: a retrospective population-based study. PLoS One 12(12):e0189233
3. Loppnow H, Zhang L, Buerke M, Lautenschläger M, Chen L, Frister A, Schlitt A, Luther T, Song N, Hofmann B, Rose-John S, Silber RE, Müller-Werdan U, Werdan K (2011) Statins potently reduce the cytokine-mediated IL-6 release in SMC/MNC co cultures. J Cell Mol Med 15(4):994–1004
4. Hansen M, Kuhlman ACB, Sahl RE, Kelly B, Morville T, Dohlmann TL, Chrøis KM, Larsen S, Helge JW, Dela F (2019) Inflammatory biomarkers in patients in Simvastatin treatment: No effect of co-enzyme Q10 supplementation. Cytokine 113:393–399. https://doi.org/10.1016/j.cyto.2018.10.011
5. Davaro F, Forde SD, Garfield M, Jiang Z, Halmen K, Tamburro ND, Kurt-Jones E, Fitzgerald KA, Golenbock DT, Wang D (2014) 3-Hydroxyl-3-methylglutaryl coenzyme a (HMG-CoA) reductase inhibitor (statin)-induced 28-kDa interleukin-1β interferes with mature IL-1β signaling. J Biol Chem 289(23):16214–16222
6. Cahill CM, Rogers JT (2008) Interleukin (IL) 1beta induction of IL-6 is mediated by a novel phosphatidylinositol 3-kinase-dependent AKT/IkappaB kinase alpha pathway targeting activator protein-1. J Biol Chem 283(38):25900–25912
7. Schauer IG, Zhang J, Xing Z, Guo X, Mercado-Uribe I, Sood AK, Huang P, Liu J (2013) Interleukin-1β promotes ovarian tumorigenesis through a p53/NF-κB-mediated inflammatory response in stromal fibroblasts. Neoplasia 15(4):409–420
8. Browning L, Patel MR, Horvath EB, Tawara K, Jorcyk CL (2018) IL-6 and ovarian cancer: inflammatory cytokines in promotion of metastasis. Cancer Manag Res 10:6685–6693
9. Yousefi H, Momeny M, Ghaffari SH, Parsanejad N, Poursheikhani A, Javadikooshesh S, Zarrinrad G, Esmaeili F, Alishahi Z, Sabourinejad Z, Sankanian G, Shamsaiegahkani S, Bashash D, Shahsavani N, Tavakkoly-Bazzaz J, Alimoghaddam K, Ghavamzadeh A (2019) IL-6/IL-6R pathway is a therapeutic target in chemoresistant ovarian cancer. Tumori 105(1):84–91. https://doi.org/10.1177/0300891618784790
10. Samavati L, Rastogi R, Du W, Hüttemann M, Fite A, Franchi L (2009) STAT3 tyrosine phosphorylation is critical for interleukin 1 beta and interleukin-6 production in response to lipopolysaccharide and live bacteria. Mol Immunol 46(8–9):1867–1877