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Comment on "Local Accumulation of FOXP3 $^{+}$ Regulatory T Cells: Evidence for an Immune Evasion Mechanism in Patients with Large Condylomata Acuminata"

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Letters to the Editor

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Comment on "Local Accumulation of FOXP3$^+$ Regulatory T Cells: Evidence for an Immune Evasion Mechanism in Patients with Large Condylomata Acuminata"

We read the interesting paper by Dr. Cao and colleagues on the role of local regulatory T cells (Tregs) in immune evasion in patients with large condylomata acuminata (1). We suggest that the cholesterol-lowering statin drugs may play a putative role in human papillomavirus (HPV) infection and subsequent genital condylomata propagation.

Statins have been shown to significantly increase the peripheral numbers and functionality of Tregs in vivo by inducing the transcription factor, forkhead box P3 (2). This may further enhance the local immunosuppressive effect of Tregs within the condylomata. Additionally, statins alter cholesterol synthesis in keratinocytes (3) and, as a result, may impair cutaneous permeability barrier function, facilitating HPV infection.

Moreover, the immunosuppressive effect of statins, by increasing Treg numbers and function, may allow the persistence of HPV type 16 and the progression of viral-induced intraepithelial neoplasia (4). Physicians need to be vigilant for the worsening of HPV in patients on statin therapy. This is of particular importance, since the American Academy of Pediatrics has recently proposed using statins in some children as early as 8 years of age (5).

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Response to Comment on "Local Accumulation of FOXP3$^+$ Regulatory T Cells: Evidence for an Immune Evasion Mechanism in Patients with Large Condylomata Acuminata"

Forkhead box P3-positive (FOXP3$^+$) regulatory T (Treg) cells play a critical role in virus-infected diseases (1). In our recent work (2) we showed that FOXP3$^+$ regulatory T cells presented in warts in patients with condylomata acuminate, leading to an immune evasion of human papillomavirus. One interesting finding in our study was cyclophosphamide. Administration of low dose cyclophosphamide (CY) could reverse Treg cell-mediated immunosuppression by selectively depleting patients' Treg cells. In line with these data, the result from our current clinical trial further demonstrates that treatment with low-dose CY decreases the recurrence of a wart after laser surgery (our unpublished data). Therefore, CY represents a new strategy in genital wart treatment. However, this may be on one side of the regulation of Treg cells. Just as the comment "statins might enhance human papillomavirus infection" by Drs. Goldstein, Mascitelli, and Pezzetta, the genital wart treatment might be hindered by a cholesterol-lowering drug statin, which is opposite to CY and increases the peripheral functional Treg cells.

Statin, the inhibitor for 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, exerts cholesterol-lowering and anti-inflammatory effects. The latter may be ascribed to its inducing the expression of FOXP3 in T cells, leading to the increase of Treg cells (3). In this regard, we totally agree with the comment from Dr. Goldstein et al. that "physicians need to be vigilant for worsening of HPV in patients on statin therapy." Nevertheless, clinical studies should be needed to fully address such questions. Regardless of its potent impediment in genital wart treatment, statin seems to palliate some inflammation-associated diseases such as multiple sclerosis (4). In addition, it will be interesting to test the possible curative effect of statin in allergic diseases, the prevalence of which has increased strikingly in the past decade.

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