EDITORIAL

Smoking in antineutrophil cytoplasmic antibody–associated vasculitis: from disease susceptibility to long-term prognosis

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Among the diverse spectrum of autoimmune conditions, antineutrophil cytoplasmic antibodies (ANCAs)–associated vasculitides (AAV) stand out as a group of rare, yet severe, disorders that target the body's small blood vessels, resulting in inflammation and damage.[1] These conditions share the presence of ANCAs as a common feature that plays a central role in their pathogenesis. Risk factors for AAV are not fully understood, albeit pathogenesis is mainly driven by the interaction between environmental and genetic factors.[2] Moreover, little is known regarding the interaction of ANCA formation and specific risk factors, owing to the paucity of animal models for translational studies.[3] Smoking, a well-established risk factor for numerous diseases, has been responsible for over 200 million deaths in the past 3 decades.[4] Recent findings suggest that the impact of smoking on mortality may be significantly underestimated, with associations emerging between smoking and increased mortality in diseases not traditionally attributed to tobacco use.[5] Whether this is the case for AAV, remains a subject of intense debate. While a recent study conducted in the United States identified smoking as a risk factor for AAV, previous European studies have reported conflicting results, some suggesting its protective effect or no effect at all.[6-9] The rarity of AAV places significant constraints on conducting prospective observational studies to assess the impact of smoking exposure. The most reliable evidence thus far comes from case-control studies, but even with large patient cohorts, the connection between smoking and severe outcomes remains elusive.

With respect to AAVs, smoking was shown to be a risk factor for the disease development in a recent study conducted in the United States on patients with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA); previous European studies reported conflicting results, some suggesting a protective effect of smoking or no effect at all.[6-9] With regard to eosinophilic granulomatosis with polyangiitis (EGPA), a recent multivariable logistic regression analysis showed that a history of smoking was independently associated with a lower risk of developing the disease, with odds ratio of 0.39 (95% CI, 0.22–0.69).[10] Overall, the effect of smoking on AAV susceptibility remains unclear.

However, the impact of smoking on the disease severity and prognosis can be independent of its effect on the disease susceptibility. In this issue of *Polish Archives of Internal Medicine*, Patel et al[11] investigated the effect of smoking on the disease activity and overall survival in a cohort of 223 AAV patients. The study included only the patients with MPA and GPA, while those with EGPA were excluded. The authors demonstrated that ever smokers (ie, the patients exposed to smoking during their lifetime, thus including current and former smokers), displayed significantly greater disease activity at diagnosis and poorer overall survival than never smokers. The disease phenotype was similar in ever and never smokers, but when a survival analysis was conducted, a greater mortality probability was observed in the former group (hazard ratio [HR], 2.89; 95% CI, 1.47–5.72; $P = 0.002$). A multivariable Cox regression model confirmed that being an ever smoker is an independent predictor of mortality (HR, 2.39; 95% CI, 1.11–5.54; $P = 0.003$). No difference in mortality was found between the former and current smokers. A drawback of this study is the lack of quantitative data regarding smoking exposure (ie, pack-years), but it must be noticed that it is

usually hard to get reliable data on this. Whether smoking is the sole environmental determinant of prognosis obviously remains unclear, as other environmental exposures (eg, asbestos) may occur more frequently in people exposed to smoking than in never smokers.[12]

Assessing the magnitude of smoking exposure as a susceptibility or prognostic factor can be challenging due to various reasons, including long latency periods, several confounding variables, dosage, and duration of exposure. Given the systemic nature of AAVs, this challenge is particularly hard to address. To further unravel the intricate relationship between smoking and AAV, there is a growing need for more translational studies that delve into the molecular effects of smoking on the body. Understanding the molecular mechanisms at play can provide crucial insights into the development and progression of such conditions, ultimately paving the way for better designed epidemiologic studies, targeted therapies, and preventive measures. Moreover, it is essential to underscore the significance of quitting and never starting smoking for overall health. As we navigate through the complexity of the impact of smoking on diseases, it becomes increasingly evident that not smoking not only lowers the risk of developing various illnesses but also improves the prognosis for those already affected. Public health campaigns and individual efforts to encourage smoking cessation are pivotal in promoting a healthier future and reducing the burden of autoimmune conditions and other associated health risks.

ARTICLE INFORMATION

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