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Insights into the paradoxical effect of smoking on vasculitis: A comprehensive review

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Abstract. Vasculitis is a group of uncommon diseases characterized by inflammation of blood vessels, which contributes to the organ ischemia and damage. Cigarette smoke contains a high concentration of various toxins, which have the potential to affect the immune response and development of autoimmune/autoinflammatory rheumatic diseases including vasculitis. Smoking influences both innate and adaptive immune systems and plays binary functions in modulating immunity by either aggravating pathogenic immune responses or attenuating defensive immunity. Smoking contributes to the pathogenesis of autoimmune diseases by various mechanisms including induction of tissue damage and apoptosis, changes in innate immune function and production of pro-inflammatory cytokines, changes in humoral immunity and T cell responses and anti-estrogen effects. In this review, we considered the available evidence on the association between smoking with the risk, clinical manifestations, response to treatment and outcomes of vasculitis, and the effect of smoking cessation on these parameters. In conclusion, despite inconclusive evidence of an increased risk of giant cell arthritis and anti-neutrophil cytoplasmic autoantibody associated vasculitis (AAV) in smokers, there is strong evidence that smokers have a lower risk of Behçet's disease (BD). Furthermore, smoking changes the clinical picture and outcomes of BD and AAV.

Key words: autoimmune/autoinflammatory rheumatic diseases (AIRDS), vasculitis, Behçet's disease, environmental factors, smoking, tobacco, cigarette smoke

Introduction

Vasculitis is a group of uncommon diseases characterized by inflammation of blood vessels, which contributes to the organ ischemia and damage. Vasculitis affects individuals of all ages and is defined based on the predominant size of the vessel involved such as large vessel vasculitis [Takayasu arteritis and giant cell arteritis (GCA)], medium vessel vasculitis (polyarteritis nodosa and Kawasaki disease), small vessel vasculitis [anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), IgA vasculitis, and hypocomplementaemic urticarial vasculitis] and Behçet disease (BD) (1). Vasculitis has unclear etiology; however, environmental factors along with genetic and epigenetic parameters play an important role in the pathogenesis of vasculitis (2). Environmental factors including microbial agents, vitamin D deficiency, diet, medications, ultraviolet light, smoking and chemicals, may contribute up to 70% to the loss of immune system tolerance and development of autoimmunity (3).

Cigarette smoke contains a high concentration of various toxic elements such as tar, nicotine, carbon

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monoxide (CO) and polycyclic aromatic hydrocarbons, etc., which have the potential to affect the immune response and development of autoimmune/autoinflammatory rheumatic diseases (AIRDs) including vasculitis (4). Smoking influences both innate and adaptive immune systems and plays binary functions in modulating immunity by either aggravating pathogenic immune responses or attenuating defensive immunity (5). Some stimulatory changes in the innate immunity response are increasing neutrophil count, enhancing neutrophil proteolytic enzyme activity such as neutrophil elastase, cathepsin G, and protease-3, elevating the expression of proteinase 3 and cell adhesion molecules by endothelial cells, enhancing expression of toll-like receptor 2 (TLR2) and TLR4 on macrophages and dendritic cells (DCs) and increasing expression of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-17 in the airway mucous (5,6). Cigarette smoke stimulates the production of free radicals that interfere with signal transduction pathways important in immune system function, including the mitogen-activated protein kinase (MAPK), nuclear factor-κβ (NF-κβ) pathway and Janus kinase/signal transducers and activators of transcription (JAK-STAT) (7). Some inhibitory effects of cigarette smoke on the innate immunity response are inhibiting formation of free oxygen radicals by neutrophils, decreasing migration and chemotaxis of neutrophils, reducing macrophage activity against intracellular organisms, suppression of DCs maturation and decreasing IL-6, IL-8, and IL-10 production (8). The inhibitory effects of smoking are caused by nicotine, hydroquinone, and CO present in the smoke (8). Smoking causes changes in multiple faces of T cell response including increasing the number of T helper (Th)1, Th17 and B cells, alteration in CD4:CD8 ratio, increasing Th2 cytokines secretion, inhibiting regulatory T (Treg) cells function, and changing the immune response to Th2 (5,6,8). It has been reported that CD4:CD8 ratio is high in light smokers (<50 pack/year) (9) and low in heavy smokers (>50 pack/year) (10). Although smoking is associated with an increased percentage of Th1 and Th17 cells in lung, which predispose to chronic pulmonary inflammation, activation of the α7 nicotinic acetylcholine receptor on macrophages, T cells and B cells by nicotine suppress Th1 and Th17 responses and shifts the immune response towards the Th2 lineage (11,12).

Despite the extensive impact of smoking on immune system function, only the role of smoking in the pathogenesis of two AIRDs including systemic lupus erythematosus and rheumatoid arthritis has been proven (4,13), while there are conflicting data on vasculitis (14). There is even more uncertainty about the association between smoking and clinical manifestations and prognosis of vasculitis (15-18). In this review, we considered the available evidence on the association between smoking and the risk, clinical manifestations, response to treatment and outcomes of vasculitis and the effect of smoking cessation on these parameters.

Smoking and risk of vasculitis

The majority of studies have shown that smoking does not increase the risk of developing primary systemic vasculitis except for AAV and GCA (Table 1). A case-control study did not report significant associations between smoking and primary systemic vasculitis (14). In a study we conducted in the Azeri population, smoking was not significantly associated with an increased risk of primary systemic vasculitis (19). In another case-control study in France, smoking was not associated with risk of AAV (20). Haubitz et al. reported lower proportion of smokers among patients with AAV compared with general German population (14% versus 14.3%) (21). However, the main limitation of these studies was the relatively small sample size. A recent case-control study of 473 cases and 1419 matched controls found that ever, current and past smoking were associated with an increased risk of AAV with odds ratios (ORs) of 1.7, 2.7 and 1.6, respectively (22). In addition, a strong dose-response relationship was observed between smoking and AAV (22). Although a cohort study reported a lower risk of GCA in male ever smokers with an incidence rate ratio (IRR) of 0.5 (23), a systematic review and meta-analysis found increased risk of GCA in current smokers (OR: 1.2) (24). Another cohort study in Norfolk, UK reported an increased risk of GCA (OR: 2) but not polymyalgia rheumatica (PMR) in smokers (25). Despite controversy in the role of smoking as a risk factor for vasculitis, there is evidence that smoking affects the phenotype of vasculitis (Table 1). Analysis of data from the French Vasculitis Study Group (FVSG) registry on AAV showed that current smokers were

Table 1. Studies on the risk of vasculitis in smokers.

Study	Country	Type of vasculitis	Type of study	Sample size	Risk of vasculitis	OR/HR/RR	Dose response
Lane et al. (14) 2003	UK	AAV	Case-control study	75	Not increased	-	-
Khabbazi et al. (19) 2019	Iran	PSV	Case-control study	126	Not increased	-	-
Beaudreuil et al. (20) 2005	France	AAV	Case-control study	60	Not increased	-	-
Haubitz et al. (21) 2005	Germany	AAV	Retrospective	197	Decreased	-	-
McDermott et al. (22) 2020	USA	AAV	Case-control study	473	Increased	2.7	Exist
Tomasson et al. (23) 2018	Iceland	GCA	Cohort study	19241	Decreased	0.5 (0.3-0.8)	-
Brennan et al. (24) 2017	USA	GCA	Systematic review	-	Increased	1.2 (1.0- 1.4)	-
Malek Mahdavi et al. (27) 2019	Iran	BD	Case-control study	192	Not increased	1.5 (0.8-2.6)	-
Lee et al. (28) 2019	South Korea	BD	Cohort study	22,995,024	Decreased	0.29 (0.27-0.31)	Exist

Abbreviations: OR odds ratio; HR, hazard ratio; RR, relative risk; UK, United Kingdom; AAV, ANCA associated vasculitis; PSV, primary systemic vasculitis; GCA, giant cell arthritis; BD, Behçet's disease.

more likely to develop Granulomatosis with polyangiitis (GPA) and less likely to develop eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA) compared to never smokers (26).

Despite numerous reports on the association between clinical manifestations of BD and smoking, there are few studies on smoking and the risk of BD (Table 1). In a cross-sectional study, we evaluated smoking rates among BD patients with two matched groups of first-degree relatives of BD patients and healthy controls (27). There was no significant difference in smoking rate between BD patients and control groups (27). Later in a nationwide population-based study in Korea, the incidence of BD between 2012 to 2016 was assessed in subjects aged 20 years and older who received a health examination arranged by the Korean national insurance between 2009 and 2012 (28). Analysis of data showed lower risk of BD in current smokers (HR: 0.3) and past smokers (HR: 0.5) compared with never smokers (28). The incidence rates of BD per 10000 person-years were 1.4 in never smokers, 0.7 in past smokers and 0.4 in current smokers (28).

Effect of smoking on clinical manifestations and severity of vasculitis

Despite conflicting data exist about the effect of smoking on clinical manifestations of vasculitis, there are many reports about the effect of smoking on the clinical picture of AAV (Table 2). Benarous et al. reported younger age, more frequent skin involvement and less frequent upper airway involvement in ever smokers among GPA patients (26). They also reported younger age, less frequent constitutional symptoms, arthralgias, renal involvement and positive P-ANCA in ever smokers among EGPA patients (26). In a study, it is stated that diffuse alveolar hemorrhage is 4 times more likely to occur in AAV patients who smoke than in never smokers (29). In a retrospective study on patients with AAV, there was no significant difference in the clinical manifestations of the disease in ever smokers and never smokers (30). However, in smokers, the time from symptom onset to diagnosis was shorter and disease activity was higher (30). Cox et al. studied low attenuation areas as a marker of obstructive airway disease in patients with AAV (31). This phenomenon

Table 2. Studies on the clinical manifestations, laboratory findings and activity of vasculitis in smokers.

Study	Country	Type of vasculitis	Type of study	Sample size	Clinical manifestations	Disease activity	Laboratory findings
Benarous et al. (26) 2015	France	AAV	Retrospective	1165	Younger age, male gender, less frequent renal involvement and less frequent EGPA and MPA in CS	Lower BVAS jn CS	More frequently C-ANCA and less frequently P-ANCA in CS
Andreiana et al. (29) 2015	Romania	AAV	Retrospective	75	4 times higher the risk of lung hemorrhage in smokers	-	-
Cox et al. (31) 2020	USA	AAV	Cross sectional	100	Slightly higher frequency of obstructive airway disease in CS	-	-
Ren et al. (32) 2022	China	AAV	Retrospective	212	Lower frequency of bronchiectasis in CS	-	-
Patel et al. (30) 2023	Poland	AAV	Retrospective	223	Shorter time from symptom onset to diagnosis in smokers	Higher BVAS in smokers	-
Kaklamani et al. (33) 2003	Greece	BD	Cross sectional	118	Lower frequency of OAU in CS (OR=0.31)	-	-
Tuna et al. (17) 2015	Turkey	BD	Retrospective	209	Higher frequency of EN, articular, ocular and neurological involvements in smokers	Higher disease activity	-
Aramaki et al. (34) 2007	Japan	BD	Retrospective	150	Higher frequency of neurological involvements in smokers		
Lee et al. (35) 2008	Korea	BD	Retrospective	131	Higher frequency of vascular and GI involvement in smokers	-	-
Bilgin et al. (36) 2005	Turkey	BD with uveitis	Retrospective	202	No difference in location and severity of uveitis between smokers and non-smokers	-	-
Malek Mahdavi et al. (27) 2019	Iran	BD	Retrospective	192	No difference in organ involvement between smokers and non-smokers	Higher disease activity in smokers	-

Abbreviations: AAV, ANCA associated vasculitis; CS, current smoking; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; BVAS, Birmingham Vasculitis Activity Score; ANCA, antineutrophil cytoplasmic antibodies; BD, Behçet's disease; OR, odds ratio; EN, erythema nodosum; OAU, oral aphthous ulcer; GI, gastrointestinal.

was more common in AAV patients compared to healthy subjects (36% versus 19%) and the difference between the two groups was mainly observed in non-smokers (31). In a case-control study on clinical features and prognosis of bronchiectasis in patients with AAV, there were more women and fewer smokers in those with bronchiectasis as compared to those without (32).

Although smoking is not a risk factor for BD, it has a tremendous impact on the clinical manifestations of this disease. Smoking has a protective effect on oral aphthous ulcer (OAU). In a cross-sectional study, Kaklamani et al. evaluated the effect of age, gender, alcohol consumption and smoking status in the presence of frequent OAU (more than 1 per month) (33). Current smoking was the only

predictor of non-frequent OAU (OR: 0.3). Tuna et al. reported more frequency of erythema nodosum, arthritis, uveitis and neurological involvements and higher disease activity in smokers (17). A study conducted in Japan reported higher frequency of smoking in patients with chronic progressive neuro BD (NBD) compared with acute NBD and BD patients without central nervous system involvement (34). Another study in Korea showed higher frequencies of vascular and gastrointestinal involvement in smokers compared to non-smokers with ORs of 3.3 and 3.9, respectively (35). Bilgin et al. reported no significant difference in the location and severity of uveitis in smoker and non-smoker BD patients with ophthalmic involvement (36). In a recent study smoking along with male sex were independent risk factors of major organ involvement (vascular, eye, nervous system and gastrointestinal tract (37). Although, our study did not find an association between various organs involvement and smoking, disease activity in smokers was significantly higher (27).

It has been suggested that smoking by increasing nicotine and aldehydes levels which are suppressor of neutrophils function, contribute in amelioration of mucocutaneous lesions in BD (18). In addition, nicotine by binding functional nicotinic acetylcholine receptors on upper respiratory tract epithelium has a direct effect on epithelium (38). Another mechanism is anti-inflammatory effect of nicotine on keratinocytes and endothelial cells (39). In a study that incubated human keratinocytes and dermal microvascular endothelial cells (HMEC-1) with sera from patients with BD, treatment with nicotine resulted in a reduction of IL6, IL8, and vascular endothelial growth factor production by these cells (39). Genetic factors may play a role in the effect of smoking on the clinical manifestations of BD. Carrying null polymorphism of glutathione S-transferase (GST) gene which is responsible to detoxify chemicals in cigarette smoke affect the clinical manifestations of BD (41). Smoking with GSTM1 null-polymorphism was associated with a low risk of developing papulopustular lesions (OR: 0.2) and chronic arthritis (OR: 0.7) (40). Smoking with GSTT1 null-polymorphism was associated with an increased risk of venous insufficiency (OR: 2.7) and development of large vessel vasculitis (OR: 1.2) (40). An additive effect between smoking and HLA-B51+ was observed in Aramaki et al.'s report, where 85% of patients with chronic progressive NBD and 7.5% of patients without chronic progressive NBD were smokers and HLA B51+ (34).

Effect of smoking on treatment response and outcomes of vasculitis

Smoking is associated with a worse prognosis in vasculitis (Table 3). In a retrospective study on 89 patients with AAV with renal involvement, smoking (HR: 1.9) was associated with increased risk of mortality and end stage renal disease (41). In a study on 89 patients with necrotizing vasculitis including GPA, EGPA, MPA and polyarteritis nodosa (PAN), upper airway damage was significantly more prevalent in non-smokers and myocardial infarction and end-stage renal disease were more common in the current smokers (42). In a study on patients with MPA, smoking was more common in patients with interstitial lung disease than in patients without interstitial lung disease (43). In a retrospective study, smoking was associated with cutaneous ischemia (OR: 1.7) and amputation (OR: 9.1) in systemic necrotizing vasculitis (44). In a study of 223 AAV patients in Korea, although smoking was a predictor of all-cause mortality at follow-up in univariate regression analysis, it was not independently predictive in multivariate regression analysis (45). However, in a report by Patel et al. in patients with AAV, mortality was higher in smokers (HR: 2.9) than non-smokers (30). In a retrospective study on 65 patients, AAV hospitalized with pulmonary complications smoking was predictor of intensive care unit admission (OR: 5.9) (46). In another study, patients with p-AAV associated lung diseases were enrolled in a retrospective cohort study (47). Patients were categorized into five groups: usual interstitial pneumonia (UIP) pattern, non-UIP interstitial pneumonia, bronchiectasis, necrotizing granuloma, and diffuse alveolar hemorrhage (47). The UIP group had significantly more ex-smokers than the other groups and the second poorest survival (47). In the investigation of predicting factors of renal outcome, patients with renal biopsy-proven ANCA-associated glomerulonephritis were studied retrospectively (48). Smoking, alveolar hemorrhage, hypertension, initial hemodialysis and sclerotic class were associated with end stage renal disease (48).

Smoking increases the risk of infection in patients with AAV. In a nationwide, prospective study

Table 3. Studies on the response to treatment and outcomes of vasculitis in smokers.

Study	Country	Type of vasculitis	Type of study	Sample size	Response to treatment	Outcome
Caravaca-Fontán et al. (41) 2016	Portugal	AAV with renal involvement	Retrospective	87	-	Higher rate of ESRD (OR: 1.8) and mortality (OR: 1.8) in smokers
Mohammad et al. (42) 2011	Sweden	AAV	Retrospective	86	-	Higher rate of MI and ESRD in the CS; ENT damage was more common in non-smokers
Hozumi et al. (43) 2021	Japan	MPA	Retrospective	218	-	Higher rate of ILD and mortality in CS
Lega et al. (44) 2014	France	SNV*	Retrospective	1304	-	Higher rate of cutaneous ischemia (OR: 1.7) and amputation (OR: 9.1)
Yang et al. (45) 2018	China	AAV	Retrospective	248	-	Higher frequency of infection in smokers
Holguin et al. (46) 2008	Georgia	AAV hospitalized with pulmonary complications	Retrospective	65	-	Higher rate of ICU admission (OR 5.9)
Jebali et al. (48) 2020	Tunisia	AAV with renal involvement	Retrospective	37	-	Higher rate of ESRD in smokers
Watanabe-Imai et al. (49) 2016	Japan	AAV during remission induction	Prospective	156	-	Higher rate of serious infection in smokers (HR: 2.6)
Lao et al. (50) 2019	China	AAV	Retrospective	132	-	Higher rate of infection in smokers (HR: 2.4)
Lao et al. (50) 2019	China	AAV	Retrospective	132	-	Higher rate of infection (HR: 2.4) and mortality in smokers
Yamaguchi et al. (52) 2018	Japan	AAV	Retrospective	122	Lower remission rate and higher relapse rate (HR: 7.5) in smokers	Higher CVD, ESRD and mortality in smokers
Bilgin et al. (36) 2005	Turkey	BD with uveitis	Retrospective	202	No difference in time to remission and relapse between smokers and non-smokers	-
Malek Mahdavi et al. (53) 2021	Iran	BD	Retrospective	245	No difference in remission rate between smokers and non-smokers	No difference in damage rate between smokers and non-smokers
Mumcu et al. (54) 2019	Turkey	BD	Retrospective	834	-	More workday loss in smokers
El-Shebiny et al. (55) 2020	Egypt	BD	Cross sectional	182	-	Higher risk of CVD in smokers

*Including polyarteritis nodosa, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis

Abbreviations: AAV, ANCA associated vasculitis; ESRD, end stage renal disease; OR, odds ratio; MI, myocardial infarction; ENT, ear, nose, throat; MPA, microscopic polyangiitis; CS, current smoking; ILD, interstitial lung disease; SNV, systemic necrotizing vasculitis; ICU, intensive care unit; HR, hazard ratio; CVD, cardiovascular and cerebrovascular diseases; BD, Behçet's disease.

for patients with AAV, smoking was an independent predictor of serious infection during remission induction (HR: 2.6) (49). Two studies from China also reported increased risk of infection in patients with AAV (45,50). In contrast, a retrospective cohort study that included adult patients with primary systemic vasculitis including AAV, BD, GCA, PMR and other vasculitis reported no association between smoking and severity of COVID-19 infection (51). In a multicenter study on patients with AAV, remission rate in smokers was significantly lower than never smokers (98.5% versus 88.9%) (52). In addition, smoking was predictor of relapse (HR: 7.5) and cox proportional hazards models showed that a cumulative smoking dose of ≥ 50 pack years was significantly associated with disease relapse (52). End-stage renal disease in smokers was more common (35.2% versus 14.7%) (52). Several studies showed higher mortality rate in smoker AAV patients (42,44,50,52).

Considering the profound effect of smoking on the function of the immune system and the clinical symptoms of BD, it is possible that smoking also has an effect on the response to treatment. However, in our study on predictors of remission in BD, smoking was not a predictor of long-term remission and poor outcome (53). Bilgin et al. reported no significant differences in the average time to resolution of uveitis with treatment and the average time to uveitis recurrence in smoker and nonsmoker BD patients (36). In contrary, a multi-center study found that smoking is one of the most important factors increasing workday loss in BD patients (54). El-Shebiny et al. investigated whether modifiable cardiovascular disease risk factors differ among patients with BD and found that smoking and hypertension increase the risk of cardiovascular manifestations in these patients (55).

Effects of smoking cessation in vasculitis

Despite an extensive search of the literature, we were unable to locate any studies that specifically examined the outcome of vasculitis before and after smoking cessation. Stopping smoking may trigger mucocutaneous lesions of BD. Rizvi et al. reported recurrence of oral and genital ulcers in a BD patient after using transdermal nicotine patch for the cigarettes (18). Soy et al. reported that cessation of smoking for 1 week triggers oral aphthous ulcers, so the frequency of oral aphthous ulcer in in two groups of BD patients who had quitted smoking and those who had not quitted smoking was 66% and 25%, respectively (56).

Conclusion

Despite inconclusive evidence of an increased risk of GCA and AAV in smokers, there is strong evidence that smokers have a lower risk of BD. Some potential mechanisms regarding the role of smoking in pathogenesis of AIRDs including vasculitis are: (i) induction of tissue damage and apoptosis by formation of free radicals, release of metalloproteinases and induction of Fas expression, (ii) changes in innate immune function and production of proinflammatory cytokines, (iii) changes in humoral immunity and T cell responses and (iv) anti-estrogen effects (57). Furthermore, smoking changes the clinical picture and outcomes of BD and AAV. An important question that arises is the reasons behind the opposing effects of smoking on the risk and/or clinical manifestations. Although the reason for this paradox is not fully understood, there are potential biological mechanisms. (i) Cigarette smoke contains thousands of chemicals that can have an inflammatory and suppressive effect on the immune system (4). Part of immunosuppressive effect of tobacco smoke are related to low levels of CO in smokers which inhibit the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-8) and increase IL-10 (58). Inhibiting intracellular pro-inflammatory pathways through activating nicotinic acetylcholine receptors expressed on synoviocytes, macrophages and fibroblasts by nicotine is another explanation (59,60). (ii) Alteration in the DCs response in smokers may be a potential explanation for its paradox. DCs express TLRs and nucleotide oligomerization domain receptors that recognize pathogen-associated molecular patterns and induce T cells proliferation and polarization (61). Two types of DCs, plasmacytoid and myeloid DCs, exhibit different regulatory functions (61,62). In an experiment on DCs obtained from patients with ulcerative colitis and Chron's disease, smoke extract led to a decrease in Foxp3+ regulatory T cells in the peripheral blood of patients with Chron's disease, while these cells increased in patients with ulcerative colitis (63). This ultimately leads to an increase in IFNγ+ CD4+ Th1 cells in Chron's disease and a decrease in these cells in ulcerative colitis (63). (iii) The difference in the effect of cigarette smoke on

intestinal microbiota can be another explanation for this dilemma (64). (iv) Genes that predispose to certain AIRDs may influence the effect of smoking. An example for this is interaction between citrullination and HLA. Cigarette smoke leads to citrullination of proteins in the respiratory tract mucosa (5). Citrullinated proteins induce anti-citrullinated protein antibodies production in HLA-DRB1 shared epitope+ individuals, whereas in HLA-DR3 carriers they lead to anti-dsDNA formation (5). (v) The difference in the interaction of epigenetic mechanisms and some components of cigarette smoke in a different way in people with various AIRDs may be another explanation (64). It has been shown that 2,3,7,8-tetrac hlorodibenzodioxin in tobacco smoke stimulates the aryl hydrocarbon receptor expressed in vertebrate cells and causes demethylation of the Foxp3 and hypermethylation of the IL-17 promoter genes (64). This leads to an increase in the number of T-reg cells and a decrease in the expression of IL-17 (64).

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