Modulation of the Immune System in Cannabis Users [3]

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In Reply: Like Dr Fournier and colleagues, we are uncertain about the possibility of class-specific differences in clinical outcomes (such as stroke or myocardial infarction) among antihypertensive drugs. Although debate continues about their relative efficacies, thiazide diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and long-acting dihydropyridine calcium channel blockers have been shown to reduce the risk of stroke. However, given the results of the recently published ALLHAT trial[1] and the relative costs of the various agents, we believe that thiazide diuretics remain the agents of first choice in hypertensive patients for the primary prevention of cardiovascular and cerebrovascular disease. Furthermore, a meta-regression of 27 antihypertensive drug trials found that the reductions in stroke (as well as other cardiovascular end points) from antihypertensive therapy observed in these trials could be explained by the achieved differences in SBP.[2] Of note, this meta-regression included the CAPPP trial that Fournier et al mention.

Drs Lakshminarayan and Anderson are correct in stating that the NCEP guidelines define only stroke due to carotid artery disease as a coronary risk equivalent. Patients with ischemic stroke of other mechanisms may qualify for treatment on the basis of other risk factors of absolute LDL levels. We believe that this is consistent with our statement that patients with documented symptoms related to vascular atherosclerosis are at high risk of recurrent events and should be considered eligible for secondary prevention. Consistent with the estimates of Lakshminarayan and Anderson, we recently reported that among 119 consecutive patients with anterior circulation stroke or TIA evaluated in a stroke prevention clinic, 82% had an LDL cholesterol level higher than 100 mg/dL (2.59 mmol/L).[3] In addition, 74% of patients had hypertension, 23% had diabetes, and 21% had established coronary artery disease. One year later, only half of patients had LDL cholesterol levels of 100 mg/dL (2.59 mmol/L) or less,[3] Until better evidence is available, we believe that symptomatic atherosclerosis in any vascular bed should be considered a "coronary equivalent" and managed as such.

In response to Dr Kirshner, 4 randomized trials provide information on treatment strategies for the secondary prevention of stroke in survivors of TIA or stroke. One evaluated warfarin vs placebo (and vs aspirin),[4] 2 compared aspirin with placebo,[5-7] and 1 trial compared adjusted-dose warfarin with low-dose warfarin plus aspirin (this study was not strictly a "secondary prevention" trial because almost 40% of the patients enrolled had already experienced a thromboembolic event).[8] The data from these trials confirm a substantial benefit with adjusted-dose warfarin and a smaller but still statistically significant benefit with aspirin, as we described. While these relative benefits are similar to those seen in the trials of primary prevention for atrial fibrillation discussed above, the absolute benefit is substantially higher in patients with prior TIA or stroke given their markedly higher stroke risk at baseline.

In response to Drs Gebel and Caplan, the Antiplatelet Trialists[9] concluded that the addition of dipyridamole to aspirin did not provide any significant benefit over aspirin alone. However, this may have been due to the wide confidence intervals rather than to the lack of an effect. The authors did note that a single randomized trial found that the addition of extended-release dipyridamole to aspirin decreased the risk of death significantly. The results of ongoing trials should provide additional guidance.

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RESEARCH LETTER

Modulation of the Immune System in Cannabis Users

To the Editor: In vitro studies and experiments in animal models have found that cannabinoids modulate immune cell function.[1] However, investigations of immune effects in human subjects are scarce and contradictory. Gene expression of cannabinoid receptors in peripheral blood mononuclear cells may be altered among marijuana users.[2] Experimental data in healthy persons have found abnormalities in T lymphocyte and natural killer (NK) cell function,

but have not confirmed that these alterations might affect susceptibility to infections.[3] We sought to investigate cell-mediated immune response and cytokine release in cannabis users.

Methods. Participants were recruited by word of mouth and gave written consent to participate in the study, which was approved by our institutional ethical committee and conducted in accordance with the Declaration of Helsinki. Volunteers were deemed healthy after a full medical history and examination. They were then interviewed about their recent use of illicit drugs, and their statements were confirmed by urine testing. A psychiatric screening excluded drug abuse or dependence (except for cannabis or nicotine) or psychiatric disorders according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

A blood sample was obtained between the hours of 8 and 11 AM to determine blood cell count and differential, lymphocyte immunophenotyping, lymphocyte proliferative response to mitogenic stimulation (stimulation index with phytohemoagglutinine [SI-PHA] or concanavaline A [SI-ConA]), and levels of interleukin 2 (IL-2), interleukin 10 (IL-10), and transforming growth factor β-1 (TGFβ1), as described previously.[4] Comparisons between cannabis exposure categories were performed using χ^2 tests or analysis of variance. Multivariate linear regression models were fitted for each immune parameter to analyze the effects of cannabis consumption after adjusting for sex, as well as consumption of coffee, tobacco, and alcohol.

Results. According to total cannabis consumption and frequency of use during the previous 6 months, participants were classified as controls (n=32), occasional users (eventual to monthly use, n=13) and regular users (weekly to daily use, n=16). Sex, tobacco smoking, and alcohol consumption were unequally distributed between groups (TABLE).

Cannabis use was associated with a decrease in NK counts, lymphocyte proliferative response by SI-PHA and SI-ConA, and levels of IL-2, and an increase in levels of IL-10 and TGFβ1. No differences were found in counts of total lymphocytes or CD4, CD8, and CD19 cells (TABLE). The significant effect of cannabis consumption on immune measures persisted after multivariate analysis controlling for the possible confounding effects of sex and use of coffee, tobacco, and alcohol. A signifi-

Table. Group Characteristics and Immune Parameters in Controls and Cannabis Users

Characteristic/Parameter	Cannabis Consumption Group			*P* Value*
	Controls (n = 32)	Occasional Users (n = 13)	Regular Users (n = 16)	
Age, mean (SD), y	22 (3)	21 (1)	23 (2)	.18
Sex distribution, No (%)				
Male	23 (72)	12 (92)	6 (38)	.005
Female	9 (28)	1 (8)	10 (62)	
Coffee consumption, No (%)				
Daily	15 (47)	8 (61)	11 (69)	.32
Occasionally/none	17 (53)	5 (39)	5 (31)	
Tobacco smoking, No (%)				
Daily	4 (13)	2 (15)	4 (26)	.03
Weekly	3 (9)	3 (23)	6 (37)	
Occasionally/none	25 (78)	8 (62)	6 (37)	
Alcohol consumption, No (%)				
Daily	0	0	5 (31)	.003
Weekly	23 (72)	11 (85)	9 (56)	
Occasionally/none	9 (28)	2 (15)	2 (13)	
Immune parameters, mean (SD)				
Total lymphocytes, cells/μL	1950 (152)	1901 (141)	1862 (176)	.23
CD4 T cells, cells/μL	933 (105)	929 (160)	849 (132)	.14
CD8 T cells, cells/μL	548 (98)	574 (159)	538 (116)	.72
CD19 B cells, cells/μL	182 (61)	142 (45)	158 (76)	.13
NK cells, cells/μL	203 (82)	145 (67)	135 (103)	.02
SI-PHA, %	96 (15)	97 (25)	57 (27)†‡	<.001
SI-ConA, %	75 (17)	75 (18)	42 (26)†‡	<.001
IL-2, U/mL	10.6 (3.8)	8.6 (5.4)	5.0 (3.4)†	<.001
IL-10, pg/mL	903 (191)	1284 (327)§	1312 (365)†	<.001
TGFβ1, pg/mL	660 (172)	1450 (937)§	1629 (725)†	<.001

Abbreviations: IL-2, interleukin 2; IL-10, interleukin 10; SI-ConA, mitogenic stimulation index by concanavaline A; SI-PHA, mitogenic stimulation index by phytohemagglutinin; TGFβ1, transforming growth factor β-1.
*From χ^2 test or analysis of variance.
†Significant difference (*P*<.05) between controls and regular users, by analysis of variance post hoc Tukey multiple paired comparisions.
‡Significant difference (*P*<.05) between occasional users and regular users, by analysis of variance post hoc Tukey multiple paired comparisons.
§Significant difference (*P*<.05) between controls and occasional users, by analysis of variance post hoc Tukey multiple paired comparisons.

cant dose-response relationship was found between cannabis exposure (total life consumption, as the log-transformed number of cannabis "joints") and the decrease in counts of total lymphocytes, CD4 or NK cells, and IL-2 levels, or the increase in IL-10 levels.

Comment. Cannabis use was associated with a decrease in levels of IL-2, a T_H1-type cytokine related to cell-mediated immunity, and an increase in levels of IL-10, a T_H2-type cytokine related to humoral immunity. The decrease of proinflammatory (IL-2) cytokines and the augment of anti-inflammatory (IL-10 and TGFβ1) cytokines was associated with a marked reduction in lymphocyte functionality, and a decrease in the number of NK cells. The suppression of immediate and innate responses of the immune system together with the disruption of T_H1/T_H2 balance might increase the susceptibility and promote the progression of infectious diseases and tumors, although the clinical relevance of these findings has not been clearly demonstrated in humans.[3,5] It also has been suggested that immunomodulatory effects of cannabinoids on inflammatory and autoimmune disorders could lead to new therapeutic interventions.[6]

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