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Increased markers of inflammation after cannabis cessation and their association with psychotic symptoms

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Original Article

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Abstract

Introduction: A dysbalance of the immune system in psychotic disorders has been well investigated. However, despite a higher prevalence of cannabis (THC) consumption in patients with psychosis, few studies have investigated the impact of this use on inflammatory markers. *Methods:* One hundred and two inpatients were included in this retrospective study. Leukocytic formula, hsCRP, fibrinogen levels and urinary THC were measured, and comparisons were performed at baseline and after 4 weeks of cannabis cessation between cannabis users (THC+) and non-users (THC−). *Results:* After cannabis cessation, we found a greater increase in leucocyte level ($p < 0.01$), monocyte level ($p = 0.05$) and a statistical trend to a highest increase of lymphocyte level ($p = 0.06$) between baseline and 4 weeks in the THC+ group as compared to the THC − group. At 4 weeks, highest leucocyte ($p = 0.03$), lymphocyte ($p = 0.04$) and monocyte ($p < 0.01$) counts were found in the THC+ group, whereas at baseline no difference was found. A positive correlation was found between monocyte count at 4 weeks and baseline Positive and Negative Syndrome Scale (PANSS) negative subscore ($p = 0.045$) and between the variation of monocyte count between baseline and 4 weeks and the PANSS total score at 4 weeks ($p = 0.05$). *Conclusion:* THC cessation is associated with an increase in inflammatory markers, including white blood cell, lymphocyte and monocyte levels, which correlates with symptomatology of patients with psychosis.

Significant outcomes

- Cannabis cessation is associated with an increase of inflammation markers such as leucocytes, monocytes and lymphocytes in patients with psychosis.
- Cannabis cessation is associated not only with an increase of inflammation markers such as leucocytes, monocytes and lymphocytes but also with hsCRP level in patients with schizophrenia.
- Kinetics of monocyte levels are associated with symptomatology in patients with psychosis.

Limitations

- The retrospective design of the cohort does not allow us to conclude a potential causal relationship.
- The naturalistic design of the cohort does not evaluate other inflammatory markers than leukocytes, hsCRP and fibrinogen.
- The naturalistic design does not permit to assess the impact of cannabis potency and its exact THC/cannabidiol ratio.

Introduction

A dysbalance of the immune system in psychotic disorders has been well investigated (Khandaker *et al.*, 2015). The vulnerability-stress-inflammation model (Howes & McCutcheon, 2017; Müller, 2018; Lestra *et al.*, 2022) implies an imbalance of the microglia activation (M1/M2 pathways' homeostasis) leading to an over-expression of pro-inflammatory cytokines (Howes & McCutcheon, 2017). This imbalance could be due to microglia priming,

including perinatal insults, early life stresses or genetic vulnerabilities, which leads to a pro-inflammatory M1 phenotype (Boksa, 2010; Sominsky *et al.*, 2012; Diz-Chaves *et al.*, 2013; Hagberg *et al.*, 2015) (5–8) and an overactivation/unregulated synaptic pruning especially in the prefrontal cortex and hippocampus, which may explain the negative and cognitive symptoms of schizophrenia (Boksa, 2010; Nestor *et al.*, 2013; Sui *et al.*, 2015; Howes & McCutcheon, 2017). Moreover, this microglial overactivation could lead to an increased disinhibition of subcortical dopamine neurons, which is thought to underline the development of positive symptoms (Grace, 2012; Kim *et al.*, 2015; Howes & McCutcheon, 2017).

The prevalence of cannabis consumption in patients with psychosis (more than 25%) is higher than in general population (Hunt *et al.*, 2018) but the bidirectional effect of cannabis use and psychosis has not yet been elucidated. Cannabis consumption leads to a poorer functional prognosis (Krause *et al.*, 2019) and a higher rate of hospitalisations (Colizzi *et al.*, 2018). Specific characteristics of this consumption seem to be associated with the risk of psychotic disorder, particularly notably for daily and high consumption (i.e. with high THC dosage among the components) (Marconi *et al.*, 2016; Di Forti *et al.*, 2019). Indeed, there is a correlation between the intensity of cannabis consumption and the risk for psychosis (Marconi *et al.*, 2016). The age of onset of cannabis use is also associated with an earlier onset of psychosis (Di Forti *et al.*, 2014; Setién-Suero *et al.*, 2018) and an increase in psychotic disorder risk (Di Forti *et al.*, 2019).

White blood cells (WBC) count, an indirect marker of low-grade inflammation, has been associated with schizophrenia (Jackson & Miller, 2020; Mazza *et al.*, 2020). Schizophrenia and first-episode psychosis are associated not only with highest levels of blood total WBC, monocytes and neutrophils than controls (Jackson & Miller, 2020) but also higher neutrophils/lymphocytes ratio and monocytes/lymphocytes ratio (Mazza *et al.*, 2020). Moreover, specific features of monocyte cell functioning seem to be associated with schizophrenia. This includes higher gene expression of inflammatory components (Drexhage *et al.*, 2010), increased production of IL1b (Uranova *et al.*, 2017), and intracellular IL6 (Krause *et al.*, 2012).

Few studies have investigated the impact of cannabis consumption on inflammatory markers with psychiatric disorders. Recently, we have found in a small sample, that cannabis cessation increases inflammatory markers such as high sensitivity C-reactive protein (hsCRP) and lymphocyte count, as compared to non-cannabis users, cannabis users with schizophrenia display lower levels of inflammation (Romeo *et al.*, 2022). These observations were in line with other studies (Miller *et al.*, 2018; Gibson *et al.*, 2020) although with discrepancy. For example, when using a within-subject design also in a small sample, Goetz and Miller (2019) did not find any difference in total nor differential WBC levels between acutely ill patients with schizophrenia with and without cannabis use.

Given the paucity of data as well as the high prevalence of THC use in patients with psychosis, further exploration of the relationship between THC use and inflammatory markers in this population is necessary. Therefore, the objective of this retrospective study was to investigate the impact of cannabis use on inflammatory markers (WBC, hsCRP and fibrinogen levels) in a larger sample of patients with psychosis and to explore the link between these inflammatory markers and clinical symptoms.

Methods

Participants

One hundred and two inpatients were included in this retrospective study from the psychiatry and addictology department at Paul Brousse Hospital (Paris). The inclusion criteria were (i) inpatients in an acute phase of psychosis (including schizophrenia, schizoaffective disorder, first episode of psychosis (FEP), non-specific delusional disorders, bipolar disorder and major depressive disorder with psychotic symptoms); (ii) over 18 years old and (iii) available urinary THC data on admission. Exclusion criteria included neurological disorders, intellectual disability, acute infection or autoimmune pathologies, high levels of inflammatory markers at baseline (hsCRP level >20 mg/mL and/or WBC >10 Giga/L) and use of anti-inflammatory treatments. In this non-interventional retrospective cohort study only using existing data from routine care, no supplementary clinical or biological examinations were done and so this study did not change the standard of care provided to the patients. A complete information was given to all patients on the possible retrospective use of their routine care data for research purposes. All patients were informed that they could refuse to have their data used retrospectively without impacting or changing the care provided. None of the included patients refused. The study was conducted in accordance with the Declaration of Helsinki and was approved by a French national committee (N°1980120).

Data collected

Socio-demographic data, comorbidities, undergoing treatments, smoking status and body mass index (BMI) were collected. Positive and Negative Syndrome Scale (PANSS) score was assessed by a trained psychiatrist. Lipid profile, fasting blood sugar, fibrinogen, hsCRP and WBC results were collected at baseline and 4 weeks later. Urinary cannabis was also collected on admission and 4 weeks later using an immuno-enzymatic method (C800 Abbott ®).To evaluate the impact of cannabis cessation on inflammatory markers, in the THC+ group, only patients who had divided at least by two their baseline THC levels at 4 weeks and with a THC level <100 ng/mL were included.

Data analyses

Analyses were performed with Medistica.pvalue.io, a graphic user to the R statistical analysis software for scientific medical publications (Available on: https://www.pvalue.io). The normal distribution of the different data sets was evaluated by a Shapiro–Wilk test. For samples including more than 30 patients with normal distribution of parameters, a *t*-test was used to compare patients in the THC+ group versus THC− group. If we had a smaller number of patients (<30 patients) and/or the data distribution was not normal, we used a Mann–Whitney non-parametric test. For categorical variables, a Chi-square or Fisher test was used. To assess the association between inflammatory markers and sociodemographic or PANSS score, Spearman or Pearson correlations were computed. A multivariate analysis was performed by linear regression including confounding factors such as age, gender, BMI, smoking statusand diagnosis.

Because more than 50 patients with schizophrenia were included, a subgroup analysis was also performed including only these patients. Given the small number of our sample, we chose to perform two models for the multivariate analysis: (i) the first one including available factors that are well known to be

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Table 1. Baseline characteristics of patients with psychosis

		THC − ($n = 65$)	THC + ($n = 37$)	p
Age, mean		40.4 (±13.7)	32.1 (±9.85)	**<0.001**
Sex ratio, M/F		45 (69%)/20 (31%)	29 (78%)/8 (22%)	0.32
Tobacco smokers		23 (38%)	35 (95%)	**<0.001**
BMI		24.7 (±4.52)	22.2 (±3.59)	**<0.01**
Diagnosis	SCZ	29 (45%)	19 (51%)	**<0.01**
	BD	15 (23%)	4 (11%)	–
	SCZ aff	10 (15%)	6 (16%)	–
	FEP	2 (3.1%)	8 (22%)	–
	MDD with psychotic features	5 (7.7%)	0 (0%)	–
	Other psychotic disorders	4 (6.2%)	0 (0%)	–
Drug Free		20 (31%)	12 (32%)	0.86
Drug Naive		21 (32%)	14 (38%)	0.57
Medication at baseline		AP ($n = 18$)	AP ($n = 10$)	0.94
		MS ($n = 6$)	MS ($n = 0$)	0.084
		AD ($n = 10$)	AD ($n = 3$)	0.37
		BZD ($n = 7$)	BZD ($n = 1$)	0.25
PANSS tot		88.2 (±22.3)	82.3 (±20.9)	0.22
PANSS pos		25.2 (±8.58)	24.5 (±8.83)	0.73
PANSS neg		20.5 (±9.25)	18.4 (±7.72)	0.24
PANSS gen		42.4 (±11.7)	39.4 (±8.31)	0.16
Glucose		5.05 (±0.83)	4.88 (±1.3)	0.5
Total Cholesterol		4.63 (±0.94)	4.58 (±0.91)	0.79
LDL		2.63 (±0.84)	2.85 (±0.84)	0.51
HDL		1.28 (±0.29)	1.23 (±0.33)	0.48
Triglycerides		1.31 (±0.77)	1.25 (±0.83)	0.71

SCZ: schizophrenia, SCZ aff: schizoaffective disorder, FEP: First episode psychosis, MDD: Major depressive disorders, BD: Bipolar disorder, THC: tetrahydrocannabinol, BMI: Body Mass Index, AP: antipsychotic, AD: antidepressant, MS: mood stabiliser, BZD: Benzodiazepine, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol.

pro-inflammatory: smoking status and BMI as covariates and (ii) the second including patients' main intrinsic factors: gender and age as covariates.

Results

Psychosis patients

Description of the population

One hundred and two patients with psychosis were included in this study (65 THC− vs 37 THC+) at baseline and 68 attended follow-up at 4 weeks (48 THC− vs 20 THC+). The main characteristics of this population are described in Table 1. BMI was higher in the THC− group (24.7 vs 22.2; $p < 0.01$), patients were older in the THC− group (40.4 vs 32.1 years; $p < 0.001$). A lower proportion of tobacco smokers was found in the THC− group (38% vs 95%; $p < 0.001$). The diagnosis repartition was also different between the two groups ($p < 0.01$). We did not find any difference between the two groups regarding gender, PANSS total score and subscores. The groups did not differ in the type of treatment at baseline.

THC and markers of inflammation

At baseline

We found highest total WBC ($p = 0.04$), lymphocyte ($p = 0.01$) and monocyte ($p = 0.01$) counts in the THC + group. No difference was found neither for neutrophil, basophil, eosinophil and platelet counts, nor for fibrinogen level or the proportion of patients with CRP level above 3 mg/L. When considering confounding factors such as age, gender, smoking status, BMI and diagnosis, the results did not persist (Table 2 and Fig. 1A).

At 4 weeks

We found highest WBC ($p = 0.02$), lymphocyte ($p < 0.01$) and monocyte ($p = 0.01$) counts in the THC + group. No difference was found neither for neutrophil, basophil, eosinophil and platelet counts, nor for fibrinogen level or the proportion of patients with CRP level above 3 mg/L. When considering confounding factors such as age, gender, smoking status, BMI and diagnosis, all the differences found in univariate analysis remained significant, respectively, for WBC ($p = 0.03$), lymphocyte ($p = 0.04$) and monocyte ($p < 0.01$) counts. Between baseline and 4 weeks, we

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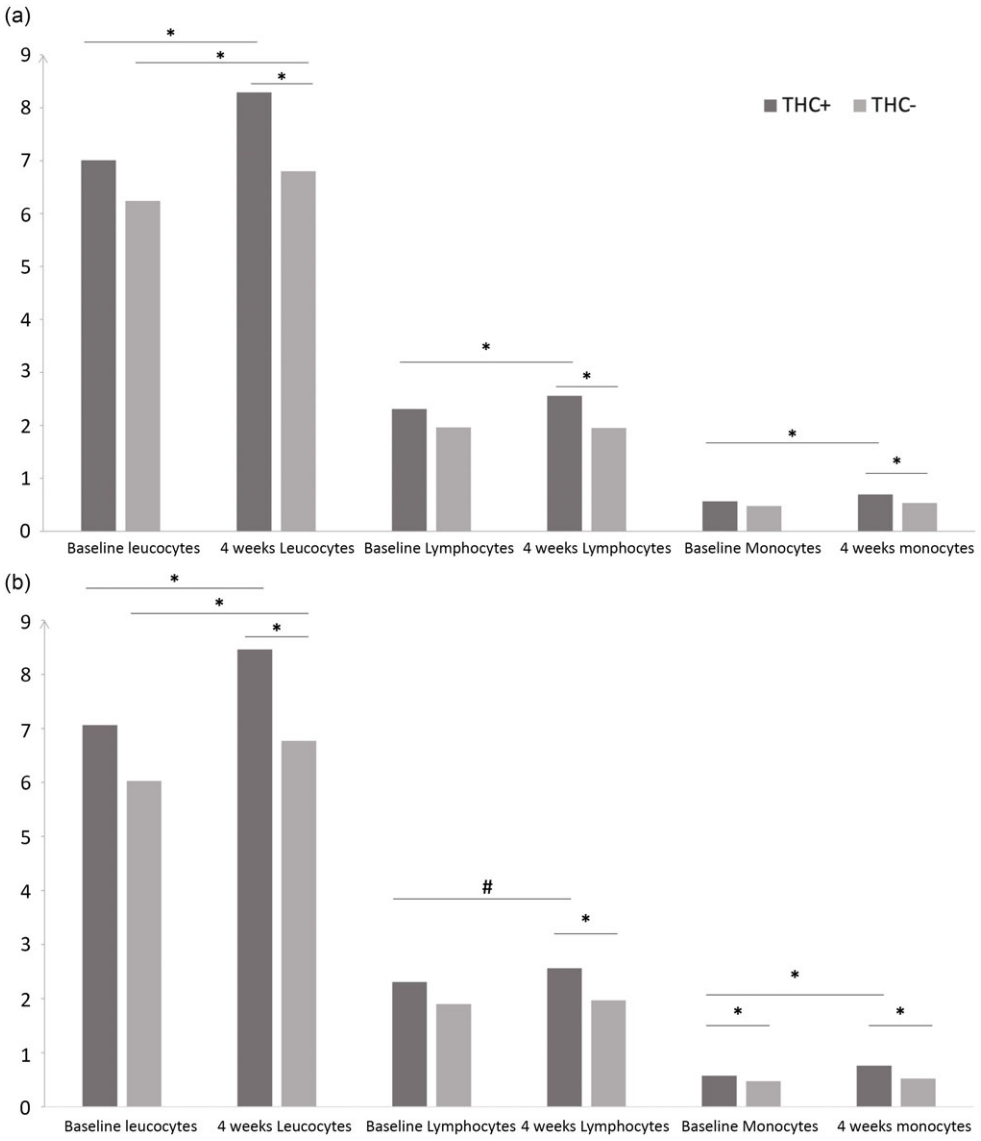

Fig. 1. A. Variations of leucocyte, lymphocyte, monocyte levels in patients with psychosis THC + and THC− between baseline and at 4 weeks. No difference was found between THC + and THC− groups at baseline for leucocyte, lymphocyte, monocyte levels. Higher levels were found in THC + for leucocyte, lymphocyte and monocyte levels, than in THC− at 4 weeks. Significant increase between baseline and 4 weeks were found in THC + group for leucocyte, lymphocyte and monocyte levels. Significant increase was found between baseline and 4 weeks in THC − group for leucocyte levels. B. Variations of leucocyte, lymphocyte, monocyte levels in patients with schizophrenia THC + and THC− between baseline and at 4 weeks. A lower level of monocytes was found in the SCZ THC− group as compared to the SCZ THC + group at baseline. Higher levels were found in SCZ THC + than in SCZ THC− at 4 weeks for leucocytes, lymphocytes and monocytes. Significant increase between baseline and 4 weeks were found in SCZ THC + group for leucocyte, monocyte levels and a statistical trend to an increase was found for lymphocyte level. Significant increase was found between baseline and 4 weeks in SCZ THC− group for leucocyte levels. * $p < 0.05$; # $p = 0.06$.

found a significant increase of WBC ($p < 0.01$), lymphocyte ($p = 0.01$), monocyte ($p < 0.01$) eosinophil ($p < 0.01$) and neutrophil ($p = 0.04$) counts in the THC + group and a significant increase of WBC ($p = 0.01$), eosinophils ($p < 0.01$) and platelets ($p = 0.04$) in the THC− group (Table 2 and Fig. 1A). This increase of leucocyte level ($p = 0.01$), lymphocyte level ($p < 0.01$) and monocyte level ($p = 0.03$) between baseline and 4 weeks follow-up was greater in the THC + group than in the THC− group. These differences remained significant when accounting for confounding factors such age, gender, smoking status, BMI and diagnosis for leucocyte level ($p < 0.01$) and monocytes ($p = 0.05$), with persistent statistical trends for lymphocyte ($p = 0.08$) levels (Table 2).

Correlation between baseline inflammatory markers and clinical variables

In the THC + group at baseline, we found a negative correlation between lymphocytes count and PANSS negative subscore ($r = -0.383$; $p = 0.04$). We found a negative correlation between fibrinogen level and PANSS general subscore at baseline ($r = -0.421$; $p = 0.036$) or at 4 weeks ($r = -0.537$; $p = 0.02$) and with PANSS total ($r = -0.537$; $p = 0.02$) or PANSS positive subscore ($r = -0.618$; $p < 0.01$) at 4 weeks.

Correlation between inflammatory markers at 4 weeks and clinical variables

In the THC + group, we found a negative correlation between lymphocyte count and baseline PANSS general subscore ($r = -0.497$; $p = 0.03$). We found a positive correlation between monocyte count and baseline PANSS negative subscore ($r = 0.452$; $p = 0.045$). We found a statistical trend for a positive correlation between the variation of monocyte count between baseline and 4 weeks and the PANSS total score at 4 weeks ($r = 0.443$; $p = 0.05$), the PANSS general subscore at 4 weeks ($r = 0.393$; $p = 0.09$) and the variation of PANSS general subscore ($r = 0.416$; $p = 0.07$).

Patients with schizophrenia

Description of the population

Sixty-four patients with schizophrenia were included in this study (49 in SCZ THC− vs 25 in SCZ THC+) at baseline and 45 attended

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Table 2. Summary of psychosis results

	Baseline				4 weeks				Difference Before/After					
	THC − ($n = 65$)	THC + ($n = 37$)	p univ	p adj	THC −($n = 48$)	THC + ($n = 20$)	p uni	p adj	THC −($n = 48$)	p	THC+ ($n = 20$)	p	THC + vs THC − puni	THC + vs THC − padj
Leucocytes	6.24 (± 1.80)	7.01 (±1.61)	**0.04**	0.18	6.80 (± 1.83)	8.29 (±2.46)	**0.02**	**0.03**	0.56	**0.01**	1.28	<**0.01**	**0.01**	<**0.01**
Lymphocytes	1.96 (± 0.661)	2.31 (± 0.662)	**0.01**	0.63	1.95 (± 0.567)	2.56 (±0.662)	<**0.01**	**0.04**	−0.006	0.87	0.25	**0.01**	<**0.01**	0.08
Monocytes	0.477 (± 0.144)	0.564 (±0.173)	**0.01**	0.17	0.535 (±0.177)	0.696 (±0.220)	**0.01**	<**0.01**	−0.057	0.07	0.13	<**0.01**	**0.03**	**0.05**
Platelets	259 (± 71.3)	269 (±54.9)	0.21		269 (± 72.5)	290 (± 60.9)	0.15		9.59	**0.04**	21.4	0.06	0.1	0.82
Basophils	0.0373 (±0.02)	0.0422 (± 0.02)	0.24		0.0452 (±0.029)	0.0445 (±0.024)	0.63		0.008	<**0.01**	0.002	0.12	0.92	
Eosinophils	0.195 (± 0.149)	0.219 (±0.201)	0.52		0.276 (±0.193)	0.330 (±0.135)	0.052	0.73	0.081	<**0.01**	0.111	<**0.01**	0.06	0.54
Neutrophils	3.56 (± 1.55)	3.95 (±1.23)	0.09	0.25	3.97 (± 1.64)	4.65 (±2.20)	0.33		0.410	0.07	0.702	**0.04**	0.34	
Fibrinogen	3.29 (± 0.513)	3.38 (± 0.658)	0.6		3.20 (±0.627)	3.15 (± 0.484)	0.97		−0.083	0.82	−0.225	0.48	0.24	
CRP > 3	38%	34%	0.74		41%	37%	0.76							

Adjusted for BMI, tobacco status, diagnosis and age.

Table 3. Baseline characteristics of patients with schizophrenia

		SCZ THC − ($n = 39$)	SCZ THC + ($n = 25$)	p
Age		38.4 (±12.6)	33.4 (±9.99)	0.12
Sex ratio, M/F (%)		32 (82%)/7 (18%)	22 (88%)/3 (12%)	0.73
Tobacco smokers		16 (44%)	23 (92%)	**<0.001**
BMI		24.8 (±4.93)	22.5 (±2.87)	0.086
Illness duration		11.6 (±11.6)	10.0 (±9.21)	0.93
Diagnosis	SCZ	29 (74%)	19 (76%)	0.88
	SCZ aff	10 (26%)	6 (24%)	–
Drug Free		23 (59%)	16 (64%)	0.69
Drug Naïve		10 (26%)	8 (32%)	0.58
Medication at baseline	AP	15 (38%)	9 (36%)	0.84
	MS	2 (5.1%)	0 (0%)	0.52
	AD	5 (13%)	2 (8%)	0.7
	BZD	6 (15%)	1 (4%)	0.23
PANSS tot		92.7 (±21.3)	82.3 (±23.9)	0.12
PANSS pos		26.8 (±8.38)	24.1 (±9.99)	0.3
PANSS neg		23.6 (±8.82)	19.4 (±8.26)	0.051
PANSS gen		42.3 (±11.0)	38.7 (±8.89)	0.23
Glucose		5.00 (±0.911)	4.81 (±1.43)	0.068
Cholesterol tot		4.44 (±0.942)	4.51 (±0.908)	0.83
LDL		2.45 (±0.869)	2.76 (±0.798)	0.4
HDL		1.28 (±0.295)	1.19 (±0.323)	0.31
Triglycerides		1.37 (±0.949)	1.34 (±0.987)	0.86

SCZ: schizophrenia, SCZ aff: schizoaffective disorder, THC : tetrahydrocannabinol, BMI: body mass index, AP: antipsychotic, AD: antidepressant, MS: mood stabiliser, BZD: benzodiazepine, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol.

follow-up at 4 weeks (33 in SCZ THC- vs 12 SCZ THC+). The main characteristics of this sub-population are described in Table 3. No difference was found between the two groups in terms of age, gender, BMI, illness duration, baseline medication, diagnosis or baseline PANSS total score and subscores. A higher proportion of tobacco smokers was found in the SCZ THC + group (92% vs 44%; $p < 0.01$) (Table 3).

THC and markers of inflammation

At baseline

We found highest WBC ($p = 0.024$), lymphocyte ($p = 0.021$) and monocyte ($p = 0.035$) counts in the SCZ THC + group compared to the SCZ THC− group. These differences did not remain significant when we included confounding factors such as tobacco status and BMI, except for monocyte count ($p = 0.042$) and for WBC when we included confounding factors such as age and gender (Table 4 and Fig. 1B). No difference was found between these two groups for fibrinogen, neutrophil, basophil, eosinophil and platelet counts. We also found a higher proportion of patients with a CRP above 3mg/L in the SCZ THC− ($p = 0.043$).

At 4 weeks

We found highest WBC ($p = 0.03$), lymphocyte ($p = 0.01$) and monocyte ($p < 0.01$) counts in the SCZ THC + group. These differences remained significant after adjustment for smoking status and BMI only for WBC ($p = 0.04$), lymphocyte ($p = 0.03$) and monocyte ($p < 0.01$) counts, and after adjustment for age and gender for WBC ($p = 0.02$), lymphocyte (<0.01) and monocyte (<0.01) counts. No difference was found neither for neutrophil, basophil, eosinophil and platelet counts nor for fibrinogen level or the proportion of patients with CRP above 3 mg/L. In the SCZ THC + group, between baseline and 4 weeks, we found a significant increase in WBC ($p < 0.01$), monocyte ($p < 0.01$), eosinophil ($p < 0.01$) counts and a statistical trend for lymphocyte ($p = 0.055$), basophil ($p = 0.068$) and neutrophil ($p = 0.092$) counts. In the SCZ THC− group, we found a significant increase in WBC ($p = 0.045$), basophil ($p = 0.01$), eosinophil ($p < 0.001$) counts and a statistical trend for platelet ($p = 0.07$) count (Table 4 and Fig. 1B). Higher increase of leucocyte level ($p = 0.03$), lymphocyte level ($p = 0.04$) and monocyte level ($p < 0.01$) were found in THC + group than in THC− group after 4 weeks. These differences remained significant when accounting for confounding factors such as smoking status and BMI for leucocyte ($p = 0.01$) and monocyte ($p = 0.02$) levels and statistical trends were found for lymphocyte level ($p = 0.09$). When accounting for confounding factors such as age and gender, leucocytes ($p = 0.01$), monocytes ($p = 0.03$) continued to be significantly higher in the SCZ THC + group at 4 weeks, and statistical trends were found for lymphocyte levels ($p = 0.06$) (Table 4).

Correlations between inflammation markers and clinical variables

In the SCZ THC + group, we found negative correlations between monocyte level at 4 weeks and the variation PANSS positive subscore ($r = -0.579$; $p = 0.05$) and PANSS total score ($r = -0.606$; $p = 0.037$) between baseline and 4 weeks.

Discussion

In this study, we found kinetic differences of WBC, lymphocyte and monocyte levels between patients with psychosis consumers who stopped using cannabis at 4 weeks as compared to non-consumers. Indeed, increased levels of WBCs, monocytes and lymphocytes were found at 4 weeks in patients who stopped using cannabis. We also found similar results in a subgroup of patients with schizophrenia. Furthermore, we found that monocyte levels were associated with PANSS-negative symptoms in patients with psychosis among the THC + group.

The impact of cannabis use on inflammatory markers in patients with psychiatric disorders has been evaluated in few studies (24–28) (Miller *et al.*, 2018; Goetz & Miller, 2019; Gibson *et al.*, 2020; Corsi-Zuelli *et al.*, 2021; Romeo *et al.*, 2022) (25–29). Levels of specific inflammatory markers such as IL-6, IFN-G and CRP were found to be lower among cannabis users as compared to non-users (Miller *et al.*, 2018; Gibson *et al.*, 2020). Goetz and Miller (2019) examined the effect of marijuana use on WBC counts in acutely ill inpatients with schizophrenia, using both within-subjects and between-groups designs. They did not find any significant impact of cannabis use on these markers. These results are in line with ours, as we did not find any difference at baseline between THC users and non-users. To our knowledge, our latest work is the first follow-up of selected inflammatory markers after cannabis cessation in patients with schizophrenia (Romeo *et al.*, 2022). In

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Table 4. Summary of schizophrenia results

	Baseline				4 weeks				Difference Before/After					
	SCZ THC − ($n = 39$)	SCZ THC + ($n = 25$)	p univ	p adj	SCZ THC −($n = 33$)	SCZ THC + ($n = 12$)	p uni	p adj	SCZ THC −($n = 33$)	p	SCZ THC+ ($n = 12$)	p	SCZ THC + vs SCZ THC- puni	SCZ THC + vs SCZ THC- padj
Leucocytes	6.03 (± 1.85)	7.06 (± 1.62)	**0.02**	0.17*/ **0.02****	6.71 (± 1.92)	8.46 (± 2.7)	**0.03**	**0.04***/ **0.02****	0.69	**0.05**	1.4	<**0.01**	**0.03**	**0.01***/ **0.01****
Lymphocytes	1.90 (± 0.736)	2.31 (± 0.636)	**0.02**	0.19*/ 0.06**	1.96 (± 0.631)	2.56 (± 0.64)	**0.01**	**0.03***/ <**0.01****	0.06	0.81	0.25	0.06	**0.04**	0.09*/ 0.06**
Monocytes	0.476 (±0.159)	0.574 (± 0.194)	**0.04**	**0.04***/ 0.06**	0.521 (± 0.175)	0.762 (± 0.236)	<**0.01**	<**0.01***/ <**0.01****	0.05	0.32	0.19	<**0.01**	<**0.01**	**0.02***/ **0.03****
Platelets	260 (± 70.5)	265 (± 57.9)	0.65		267 (± 73.5)	287 (± 68)	0.27		9.59	**0.04**	22.6	0.25	0.13	
Basophils	0.033 (± 0.015)	0.044 (± 0.026)	0.13		0.047 (± 0.032)	0.048 (± 0.026)	0.19		0.013	**0.01**	0.005	0.07	0.41	
Eosinophils	0.183 (± 0.123)	0.233 (± 0.234)	0.57		0.285 (± 0.205)	0.336 (± 0.153)	0.19		0.1	<**0.01**	0.103	<**0.01**	0.14	
Neutrophils	3.46 (± 1.66)	3.90 (± 1.27)	0.1		3.88 (± 1.74)	4.74 (± 2.43)	0.24		0.412	0.23	0.845	0.09	0.17	
Fibrinogen	3.26 (± 0.502)	3.37 (± 0.738)	0.65		3.24 (± 0.7)	3.19 (± 0.567)	0.94		−0.017	0.81	−0.186	0.44	0.18	
CRP > 3	42%	17%	**0.04**		56%	45%	0.57							

Adjusted for * BMI, tobacco status; ** Age, gender.

this first study, we have shown that CRP levels were lower at baseline in the SCZ THC + group, whereas no difference was observed at 4 weeks between the two groups, suggesting a restoration of low-grade inflammation after cannabis cessation. In this study, including a larger population, we confirmed these data with lowest levels of CRP in the SCZ THC + group as compared to the SCZ THC− group at baseline, and no significant difference after 4 weeks of follow-up considering the CRP levels. In our first work, we also found that lymphocyte levels were higher both at baseline and after 4 weeks of follow-up in the SCZ THC + group, with a significant increase across study period at baseline (Romeo *et al.*, 2022). We did not find the same result in this study with no difference at baseline between the THC + and THC− group. The difference in sample sizes between the two studies might explain these different results (Romeo *et al.*, 2022).

The higher level of WBCs, lymphocytes and monocytes at 4 weeks and between baseline and 4 weeks found in patients in psychosis, notably in schizophrenia with cannabis use, reinforces the idea that cannabis use acts on peripheral and central inflammation (Cabral *et al.*, 2015). The interaction between THC and CB2 receptors expressed on lymphocyte and monocyte membranes could explain the modulation of these cells' migration and cytokine production (Sexton *et al.*, 2013; Persidsky *et al.*, 2015). This interaction could explain the decrease in microglial activity, known to be increased in psychosis (Pollak *et al.*, 2016). Another hypothesis that may explain the modulation of inflammatory markers by cannabis use could be its impact on the blood–brain barrier (BBB) and intestinal permeability. Indeed, cannabis use has been associated with decreased permeability and decreased monocyte translocation across the BBB in patients with human immunodeficiency virus (Persidsky *et al.*, 2015; Ellis *et al.*, 2020). Besides, abnormalities in BBB permeability and its impact on central translocation of pro-inflammatory cytokines are known to be linked with increased intracerebral inflammation in patients with schizophrenia (Pollak *et al.*, 2018). Cannabis may affect the intestinal permeability, as observed in patients with psychosis (Ishida *et al.*, 2022). Indeed, THC decreases intestinal permeability (36–39) (Massa *et al.*, 2004; Kimball *et al.*, 2006; Alhamoruni *et al.*, 2010; Massa *et al.*, 2004) (37–40) through the tight junction proteins (Alhamoruni *et al.*, 2010). The increase in inflammatory markers after 4 weeks of cannabis cessation could also point to a resumption of BBB and gut abnormal permeability.

We also found in the THC + group that monocyte level and monocyte change across study period were correlated with the PANSS score. THC use in patients with psychosis is associated with poorer functionality (Setién-Suero *et al.*, 2018). An association between poor functioning, negative and neurocognitive symptoms in patients with psychosis has been described (Stouten *et al.*, 2017; Lee *et al.*, 2018). Interestingly, cognitive symptoms are associated with inflammatory markers in somatic and psychiatric diseases (Fourrier *et al.*, 2019) which could be explained by a dysregulation of the glutamatergic, tryptophan-kynurenine pathway and hypothalamic-pituitary axis (Fourrier *et al.*, 2019). Minocycline by reducing microglial activation has been proposed to improve cognitive impairment among schizophrenic patients (Levkovitz *et al.*, 2010). We can suspect that increased inflammation in patients with psychosis could lead to a neurocognitive deterioration as observed in HIV patients (Williams *et al.*, 2014; Hong & Banks, 2015). Cannabis use could therefore be used to counteract anxiety symptoms and therefore cognitive impairment (Schofield *et al.*, 2006; Schaub *et al.*, 2008; Dekker *et al.*, 2009). The withdrawal period is well known by clinicians as a time of high vulnerability, in particular due to the anxiety symptoms which can trigger acute relapses. Taking into account the increase in inflammation during this period could therefore open therapeutic perspectives during cannabis withdrawal for these patients.

Our study has several limitations. First, the retrospective design of the cohort does not allow us to conclude for a potential causal relationship. Furthermore, because of the retrospective design of our study, we were enabled to assess the addictological profile of the patients which could bias our data such as tobacco/cannabis, notably we did not have information on the frequency of cannabis use, the cannabis potency nor the exact THC/cannabidiol ratio. Finally, we did not study other inflammatory markers such as cytokine levels. These three limitations can be explained by the naturalistic, non-interventional design of our study using existing data from routine care and need to be replicated by other studies.

In conclusion, this study shows that cannabis cessation is associated with an increased inflammation depicted by an elevation of white blood cell, lymphocyte and monocyte levels, which correlates with symptomatology of patients with psychosis. Studying the link between cannabis and inflammation could lead to a better understanding of the pathophysiology of psychosis.

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Ethical statement. The study was conducted in accordance with the Declaration of Helsinki and was approved by a French national committee (N°1980120).

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