International Journal of Innovative Research in Engineering & Management (IJIREM)
ISSN: 2350-0557, Volume-9, Issue-1, February 2022
https://doi.org/10.55524/ijirem.2022.9.1.55
Article ID IJIR- IRP229141, Pages 277-281
www.ijirem.org

Cannabinoids' Short-Term Effects on Immune Phenotype and Function in HIV-Infected Patients: A Review

Deepti Mathpal [1], and Gulshan Rathore [3]

[1, 2] Assistant Professor, School of Medical and Allied Sciences, Sanskriti University, Mathura, Uttar Pradesh

Correspondence should be addressed to Deepti Mathpal; deepti.ips@sanskriti.edu.in

ABSTRACT: Smoking marijuana and 9-tetrahydrocannabinol (THC) (dronabinol, Marinol) is used for treating anorexia and weight loss caused by the human immunodeficiency virus-1 (HTV-1). However, there have been concerns that these chemicals may have a negative influence on the immune systems of HTV-infected persons. The writer has conducted randomised, potential, controlled trial in adults who have HIV-infection and who have been receiving protease inhibitor-that contains high active antiretroviral therapy to assess the usage of marijuana cigarette (3.95 percent THC), dronabinol (2.5 mg), and an oral placebo in adults who have HIV-infection receiving protease inhibitor-containing highly active antiretroviral therapy (HAART). Immunological presentation (flow cytometric quantification of cellular subpopulations, B cells, and natural killer [NK] cells) and immunological function (induced cytokine production, NK cell activity, and lymphoproliferation) tests were carried out at the beginning and on a regular basis.

KEYWORDS: Cannabinoids, Cells, Marijuana, HIV, Δ9-tetrahydrocannabinol (THC).

I. INTRODUCTION

Smoked marijuana was extensively used to alleviate anorexia and weight loss caused by the immunity deficiency of virus-1 of humans before the development of most active antiretroviral treatment (HAART) (HlV). Due to a lack of evidence, this was the case. The state of California passed legislation in the year 1996 which allowed doctors to prescribe marijuana for a range of health conditions which includes AIDS wasting ailment. The formation of many cannabis "buyers clubs" in the San Francisco Bay Area boosted access to smoked marijuana. Previously, such businesses were estimated to be supplying marijuana to over 10,000 HIV-positive people. Despite anecdotal claims of weight gain, greater frame of mind, and improved standard of living in their patient who were smoking marijuana, medicine practitioners who were taking care of HIV-positive patient have expressed concerns regarding the marijuana safety used by patients with immunological impairments. Researches on the consequences of marijuana on tolerance had previously been proven to be conflicting and difficult to understand when considered together. THC, the psychoactive components of marijuana, have been shown to inhibit immune system purpose such as cellular proliferation, antibodies production, natural killer (NK) cell activities as well as phagocytic functions, as well as the dysregulation of production of inflammatory cytokines for example interferon-gamma (IFN-) in addition to a tumour necrosis factor-alpha (TNF-) and confer altered vulnerability. CBl and CB2 cannabinoid receptors are discovered. The receptors of CBl, that are acts of expressing in the brain, is thought to be important in cannabis' effects on the central nervous system. The CB2 receptor, on the other hand, may be found on the facet of B lymphocytes as well as NK cells, as well as in peripheral organs such as the spleen's marginal zone. As a consequence, there's a chance THC and the immune response may interact [1].

There hasn't been any controlled study on the effect of marijuana on immunological function in HIV-positive persons yet. Marijuana has the capacity to enhance viral load, either by stimulating or suppressing immune function. Finally, despite the fact that both protease inhibitors and marijuana are digested via the cytochrome P450 enzyme system, most of the HIV-positive patients do not stop smoking marijuana and take it a smokingamma (IFN-) in addition to a219219219219219219219219219219219219219219219219219 219219219219219219219219219219219219219219219219219219 219219219219219219219219219219219219219219219219219219 219219219219219219219219219219219219219219219219219219 219219219219219219219219219219219219219219219219219219 219219s a stimulant for appetite or to reduce nausea after antiretroviral treatment. The possible side effects of a certain drug are concerning." We conducted a research to explore the welfare/noxious balance of cannabis in HIV patients on protease inhibitor-containing regimens to better understand the possibility of these side effects. The researchers wanted to see how cannabis affected HIV RNA level, the immunity system, and the pharmacokinetics of 2 commonly used protease inhibitors, indinavir & nelfinavir (both smoked and taken orally). The major conclusion was chosen because of the possibility of a link between cannabis and protease inhibitor metabolism, as well as cannabinoids and the immunity system. The immunological terminal of

this research on marijuana's short term influence on HIV-positive patients are listed below. Separate studies have been conducted on the pharmacokinetics of the protease inhibitor as well as the limited-period effects of cannabis on viral load [2].

II. LITERATURE REVIEW

The widespread use of smoked marijuana to treat anorexia that is related to HIV and loss of weight, and nausea from prescription drugs, prompted the formation of a clinical research facility in the Bay Area of San Francisco to investigate the drug's safety and effectiveness. The Community Consortium, a local HIV clinical trials group in the Bay Area, conducted the first pilot study comparing smoked marijuana versus oral tetrahydrocannabinol in 1993. (THC, also known as dronabinol or Marinol) It was almost hard to find a legal quantity of marijuana. Two further applications were submitted to the National Institute of Health in the year 1996 and 1997. Throughout this time, a growing number of HIV-positive individuals began purchasing marijuana for "medicinal reasons" via provincial Cannabis Buyer Clubs. In the year 1996 of November, voters of California approved Proposition 215, which authorised the usage of marijuana for medical uses. The federal authority's effort for overturning the will of the people was highly derided. Organized medicine has requested further research on marijuana's therapeutic potential. The consortium's suggestion in 1997 to look into the possible interactions between THC and commonly prescribed protease inhibitors was well appreciated. The National Institute on Drug Abuse has donated financing as well as the study's requisite marijuana cigarettes, and the experiment's initial volunteers are now being recruited. Politically sensitive research projects that include strong science may triumph if scientists are willing to continue [3].
Clinton A in his study discloses about the rapid onset of the AIDS pandemic, as well as the initial absence of viable therapies, galvanized the patient community into demanding that promising drugs be developed and made available sooner rather than later. The federal government's Public Health Service shut off the sole authorized source of supply when a large number of AIDS patients requested marijuana to cure anorexia and wasting condition caused by both disease and medicines. The federal government's lack of sympathy and suppression of research sparked a grassroots political movement against federal restrictions [4].
Over time, macrophages learn to recognise and react to prime and trigger signals like as gamma interferons (IFN gamma) as well as bacterial lipopolysaccharides, according to G A Cabral's studies (LPS). Excessive LPS exposure may also result in total stimulation of these cells. Each stage of activation is linked to varying degrees of protein expression, which means that freshly created proteins are linked to the stage's operational activities. Protein profiles, according to these findings, might be engaged as a barometer of macrophage activity. THC, a psychoactive part of marijuana, is reported to decrease derivable protein produced in response to the priming agents Concanavalin A (Con A) supernatant and IFN gamma. In reaction to LPS, THC lowered protein expression. In iso-Dalt two-dimensional gel electrophoresis, P388D1 as well as RAW264.7 macrophage-like cells handled with Con A supernatant or IFN gamma showed protein profile rearrangement. Protein profile alterations in LPS-treated macrophages differed from those seen in reaction to priming agents. THC (10(-7) M to 10(-5) M in combination with Con A supernatant, IFN gamma, or LPS produced protein profiles identical to unprimed or unactivated macrophages. The synthesis of P388D1 macrophage class II Ia molecule of the vital histocompatibility complexities (MHC) was decreased in response to Con A supernatant and IFN gamma, suggesting that THC alters the expression of specific proteins whose induction is related with macrophage priming or activation. THC inhibited the production of tumour necrosis factor alpha in RAW264.7 cells treated with LPS (TNF alpha). According to these findings, THC reduces macrophage functional activity by lowering their ability to generate effective compounds in reaction to prime and activate signals [5].

III. DISCUSSION

A. Population Research

Subjects must be a minimum of eighteen years old, having HIV infection verified, as well as have been on a stability antiretroviral medication authority consisting of indinavir (Crixivan, Merck) or nelfinavir for a minimum of eight weeks (Viracept, Agouron). Participants who had previously been taking a more recently prescribed dose of nelfinavir (1250 mg twice daily) were decided to switch to a dose of seven hundred and fifty miligrams thrice a day for uniformity of our pharmacokinetic evaluations upon admittance to the research centre of general hospital in San Francisco for the two 5-days inpatient court proceedings.
There were no further protease inhibitors allowed throughout the study. Subjects required to have a constant viral load for the 16 weeks before to enrolment, which was defined as a change in HIV RNA level of less than threefold (0.5 log1 0). To ensure that all participants knew how to breathe and were aware of the neuropsychiatric implications, prior marijuana smoking experience was required (defined as six or more times). The University of California, San Francisco's Committee on Human Research approved the study, and each participant submitted written informed consent before being recruited. Exclusion criteria included current drug use, methadone therapy, cigarette or cannabis use (smoking or oral) within thirty days of enrolling, a history of severe lung illness, pregnant, as well as Stage two or even a high pulmonary disease. The following were the excluded things in laboratory: Hematocrit lesser than 25% as well as hepatic transaminase levels more than five times the maximum limits of fine Megestrol acetate, nandrolone, oxandrolone, oxymetholone, human growth hormone, thalidomide, pentoxifylline, prednisone, interleukin-2, chemotherapy, radiation, or any other experimental drugs that really affect immunity system functions were not included in the study [6].

B. Examine Medications

Prerolled marijuana cigarettes weighting an average of 0.9 gramme and contains three point nine five percent THC that were given by the National Institute on the abuse of Drugs (NIDA). These smokes were stored in a secure and well-controlled freezer until they were moved to the GCRC's sealed freezer for inpatient testing. Overnight in a humidifier, the marijuana cigarettes should be rehydrated. In the smoked marijuana condition, the subjects were placed in a room with a window to the outdoors. Participants were watched while using the Foltin consistent puff technique to verify that inhaled amounts were consistent. 2 0 Before and after the marijuana cigarettes have been delivered to the participants, they were weighed, and any residual drug was transferred to the pharmacist for ultimate return to NIDA. Subjects were allowed to smoke up to three whole marijuana cigarettes per day, if permitted, one hour before meals. Dronabinol and matchin g placebo capsules were provided by Roxane Laboratories (Columbus, OH) [7].

C. Procedures and Design of Research

In a double-blind research, those who took dronabinol two point five mg or placebo on the similar schedule as marijuana-smoking individuals were randomized. In the randomized, placebo-controlled study, two inpatient stays were included. In the first phase, people were submitted to the GCRC for baseline parameter measurements after a four-day lead-in period. The presence of THC in a urine sample collected the day before admission was required (day -4). The second phase consisted of a 21-day intervention session that started on day 0 with therapeutic randomization. Participants were randomly randomized to study medicines in 12-block blocks with equal probability depending on their protease inhibitor (indinavir or nelfinavir) (marijuana, dronabinol , and placebo). During the 25-day trial, subjects were not allowed to receive visitors or depart the GCRC unless escorted by research employees. The GCRC gathered or executed all clinical laboratory testing and research activities [8].

D. Lymphocyte Counts in Absolute

Automated routine blood checkup along differential were done at Clinical Laboratory of General Hospital in San Francisco utilizing an automated haematology analyzer in accordance with the producer's instructions. Immunophenotyping Baseline specimen was taken on day zero, and follow-up samples were collected on days seven, fourteen, and twenty one [9].

E. Flow Cytometry of Cytokine

A cytokine flows cytometry test was utilised to assess the proportion of CD4+ T cells that are excited (express CD69) as well as release particular cytokines (TNF-, IFN-, or IL-2) in relation to changing CM V antigen stimuli. 2 1 Cultures which had been stimulated with the super antigen Staphylococcal enterotoxin (SEB) were considered positive controls, whereas cultures that had not been stimulated were considered negative controls. Filtered virus prepared from sentient CM V strains ADl69-infection persons foreskin fibroblast cells have always been incubated for 5 hours with heparinized blood based on an analysis concluded filtered virus prepared from human CM V strains ADl69-infection persons foreskin fibroblast cells were always incubated for 5 hours with heparinized blood based on the analysis completed (Advanced Biotechnologies, Inc., Columbia, MD). During the final 3 hours, we utilised Brefeldin A (Sigma), FACSTM lysing soln (BD Biosystems), centrifugation, as well as coprecipitation of cell in FACSTM permeabilizing soln (BD Biosystems). Flow cytometry was utilized to analyze the cells after they were tagged by monoclonal antibody that are specially for CD4, CD69, and TNF-, IFN-, or IL-2. The proportion of CD4+ cells that stain positive for CD69 and the cytokine in between the cells of issue was altered after the frequency of CD4+ cells staining positive for CD69 and the intracellular cytokine of concern was reduced after CM V stimulization. Early investigations employed a less capable of producing cell which is lysate-negative controlled preparations, a development of tissue in environment containing ten percent human AB serum, and none stimulating as control stimulants. There was no discernible difference between the negative controls[10].

F. The Role of Natural Killer Cells

K562 erythroleukemic target cells were used to investigate the cytolytic activity of N K cells. 2 2 K562 cell suspensions were labeled with 51Cr and cultured with RPMI164 0 and 10% human AB serum for 2 hours at 37°C. After centrifugation and trypan blue incubation, the cells were counted. Before plating in K562 cell at E is to T ratios of 6.3 is to 1, 12.5, 25, 50, and 100, PBMC were collected using a density gradient centrifugation, measured, and standardised to 1 10 7 cells/ml. Before being collected and counted, cultural plate were split and incubation was done for 4 hours at 37°C with five percent CO2. Net N K cell cytotoxicity and per NK cell cytotoxicity have been calculated and shown as a percentage of target cell lysis for each E:T ratio [11].

G. Lymphoproliferation

To measure lymphoproliferation, a standard tritiated thymidine uptake technique was applied. 2 and 3 PBMC were cultured in quadruplicate for 3 to 6 days with phytohemagglutinin (PHA, Sigma), tetanus toxin (Connaught Laboratories, Swiftwater, PA), CMV antigen (BioWhittaker), or a population of inactivation alloreactivity of humans PBMC before being pulsed with 1 O of tritiated thymidine. The stimulation index (SI) for each antigen was calculated by summing the numbers per minute (cpm). On a weekly basis, at least one HIV-uninfected comparison was employed throughout the study. Positive responses for that origin were detected with yet another antigen or for other donors on the same day in all cases where donor cell responses were judged to be negative [12].

H. Analytical Statistics

By comparing baseline (day 0) and post-cannabinoid therapy (day 21) data, the researchers investigated the effects of cannabis on raw lymphocyte counts,

immunophenotyping analyses, and immunological responses as measured by cytokine flow cytometry, NK cell test, and lymphoproliferation assay. The median values for these variables at baseline, as well as the average values for each arm's reaction to changes in each parameter from day 0 to day 21, are shown. Nonparametric statistical tests were used because several of the baseline and modification variables were not normally distributed. At the commencement of the experiment, Kruskal-Wallis tests were used to examine whether there were any significant differences between the placebo and cannabis groups.Based on the change in each measure from day 0 to day 21, Kruskal-Wallis tests were used to see whether there was a significant difference between the placebo and cannabis arms [13].

I. Characteristics of the Subject

62 participants participated in the study. Twenty patients were given the option of smoking marijuana, taking dronabinol, or taking a placebo. There were 55 males, three females, and four male-to-female transgendered people in the study. Half of the patients were white (n = 31), 12 were black, 10 were Latino, and 9 were of hybrid or other race. Contemporary finish half of the patients [n = 33] were aged 40 to 49, with 18 being under 40 and 11 being over 50.

J. Immunophenotyping and Absolute Lymphocytes

Over the course of the 21-day study, immunophenotyping resulting for percent CD4+ cell, percent CD8+ cells, percent naive CD4+ cells, percent ignorant CD8+ cells, percent memory/effector CD4+ cells, percent memory/effector CD8+ cells, percent CD3-CD19+ B cells, and percent CD3-CD56+ NK cells were harvested for any and all thrice of the arms. For any of these characteristics, there were no significant variations in baseline values between both the three groups. When we compared the changes in these characteristics from day zero to day twenty one, we discovered just one main difference between the cannabis and placebo groups. Absolute lymphocyte counts increased substantially more in the marijuana group when differentiated to the controlled group (median change = 300 cells/; = 0.01). For four additional immunophenotyping variables, the dronabinol arm had significantly higher baseline values than the placebo arm: percent CD4+HLA-DR+ cells (median = 11.8 vs. 4.5; = 0.03), percent CD4+CD38+HLA-DR+ cells (median = 9.0 vs. 4.5; = 0.04), and percent CD8+HLA-DR+ cells (median = 20.0 vs. The dronabinol arm showed a lower percentage of CD8+CD38+HLA-DR+ cells (median change = -3.50 vs. 0.05; = 0.001) and a lower percentage of CD8+CD69+ cells (median change = -0.3 0 vs. 0.05; = 0.04) than the placebo arm. A further decrease in the percentage of CD4+CD38+HLA-DR+ cells was statistically significant (median change = -1.2 0 vs. -0.25; = 0.06). On day 0, the percentages of CD8+CD38+HLA-DR+ and CD4+CD38+HLA-DR+ in the dronabinol arm were substantially greater than in the placebo arm in two of these three variables. As a result, the idea of baseline disparities confounding future apparent developmental differences between days 0 and 21 cannot be entirely out. We found zero statistically main variations in baseline or change throughout groups when researchers contrasted the marijuana arm's findings to the intervention arm's results for either immunophenotyping criteria [4].

K. Flow Cytometry of Cytokine

In any of the three groups, there are still no significantly different in baseline values here between placebo and cannabinoid arms, nor in modifications from day 0 to day 21. However, cytokine flow cytometry characteristics in both cannabis groups exhibited virtually totally favorable media n alterations. Only one slight negative media n change was seen in the dronabinols (CVM-stimulation CD69+/IL-2 positive cell) and cannabis arms (CVM-stimulated CD69+/TNF-oc cell) [10].

L. The Role of Natural Killer Cells

On day 0, there were no statistically significant variations in the activities of N K cell obtained from patients in the placebo and cannabis groups.

Despite the identification of many distinct patterns, there were no reliably main differences in the modulation of N K activities from day zero to day twenty one when those on dronabinol were contrasted to those on placebo. There was a net decrease in N K cell activity among dronabinol people compared to placebo users at all E:T ratios excluding 12.5:1 and 6.3:1. (0.7 vs. -0.7 and -0.7 vs. -1 . 4 , respectively).

A net positive medium was there n shift in N K cell activities amongst marijuana patient compared to those on placebo at all E:T ratios excluding median impulsive release (-4 vs. 274) and average maximal release (-4 vs. 274). (354 versus -1619). These medium n alterations were statistically significant for percent lysis, with effector-to-target ratios of 50:1 (15.5 vs. 1.8; -0.003), 25:1 (6.4 vs. -0.9; = 0.01), 12.5:1 (4.6 vs. -0.7; = 0.02), and 6.3:1 (3.0 vs. -0.7; = 0.05)[7].

M. Lymphoproliferation Assay

Usage of PHA, tetanus toxin, CM V antigen, as well as neutralization alloreactive humans PBMC, no statistically main changes or prevalent patterns were seen between the placebo and cannabis groups at the start or between days 0 and 21. When dronabinol users were compared to placebo users, only one result for median shift in SI using 100,000 alio cells/well approached statistical significance (-4.4 vs. 6.4; = 0.08) [9].

IV. CONCLUSION

Many studies on cannabis' immunological impacts have been carried out in cell culture systems or on animals. In humans, the immune function of chronic marijuana users has just been investigated. No clinical studies have been there to evaluate the immunological consequences of smoking marijuana in HIV-positive people. In retrospective analyzation of the Multicentres AIDS Cohort research results among 1662 seropositive buyers of psychoactive drug, no interventions were linked to improved clinical or immunologic indicators of infection of HIV.

89 percent of seropositive males in the study had used marijuana in the previous two years. This confirmed what

had been revealed on a previous visit to San Francisco General Hospital. Regardless of any complicating circumstances, marijuana use has been linked to an increased prevalence of bacterial pneumonia among HIV-positive intravenous drug users. Finally, the majority of the immunological indicators examined in this research indicated no indication of cannabis's negative effects. Because of the short period of this trial, our findings are constrained (21 days). Furthermore, the absence of a blind controlled team for smoking marijuana arm may bias the interpretation of few of the main research findings (e.g., changes in weight). However, any bias produced by HIV-1 RNA or lymphocyte subset effects is difficult to identify. We decided against employing a placebo group that smokes as we considered it would be difficult to blind marijuana users. Previous research on THC's effects on the immune system yielded contradictory findings, which might be related to discrepancies in study participants, drug composition, drug concentration, or assay settings. One of the most pressing questions would be whether long-term marijuana use has any immunological repercussions.

REFERENCES

[1] S. Abo-Elnazar, M. Moaaz, H. Ghoneim, T. Molokhia, and W. El-Korany, "Th17/Treg imbalance in opioids and cannabinoids addiction: relationship to NF-κB activation in CD4+ T cells," Egypt. J. Immunol., 2014.

[2] D. I. Abrams et al., "Short-Term Effects of Cannabinoids in Patients with HIV-1 Infection: A Randomized, Placebo-Controlled Clinical Trial," Ann. Intern. Med., 2003, doi: 10.7326/0003-4819-139-4-200308190-00008.

[3] B. M. Bredt, D. Higuera-Alhino, S. B. Shade, S. J. Hebert, J. M. McCune, and D. I. Abrams, "Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients," J. Clin. Pharmacol., 2002, doi: 10.1002/j.1552-4604.2002.tb06007.x.

[4] L. Brunet et al., "Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: A longitudinal Cohort analysis," Clin. Infect. Dis., 2013, doi: 10.1093/cid/cit378.

[5] D. W. Cescon, A. V. Page, S. Richardson, M. J. Moore, S. Boerner, and W. L. Gold, "Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer," J. Clin. Oncol., 2008, doi: 10.1200/JCO.2007.15.2777.

[6] C. Chao et al., "Recreational drug use and T lymphocyte subpopulations in HIV-uninfected and HIV-infected men," Drug Alcohol Depend., 2008, doi: 10.1016/j.drugalcdep.2007.11.010.

[7] M. J. Chusid, J. A. Gelfand, C. Nutter, and A. S. Fauci, "Letter: Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease.," Ann. Intern. Med., 1975, doi: 10.7326/0003-4819-82-5-682.

[8] Y. Gargani, P. Bishop, and D. W. Denning, "Too many mouldy joints - marijuana and chronic pulmonary aspergillosis," Mediterr. J. Hematol. Infect. Dis., 2011, doi: 10.4084/MJHID.2011.005.

[9] A. J. Gill and D. L. Kolson, "Chronic inflammation and the role for cofactors (hepatitis C, drug abuse, antiretroviral drug toxicity, aging) in HAND persistence," Current HIV/AIDS reports. 2014, doi: 10.1007/s11904-014-0210-3.

[10] R. Hamadeh, A. Ardehali, R. M. Locksley, and M. K. York, "Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient," Chest, 1988, doi: 10.1378/chest.94.2.432.

[11] C. Hézode et al., "Erratum: Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C (Hepatology (2005) 42 (63-71))," Hepatology. 2005, doi: 10.1002/hep.20774.

[12] A. Jatoi, J. ichi Yamashita, J. A. Sloan, P. J. Novotny, H. E. Windschitl, and C. L. Loprinzi, "Does megestrol acetate down-regulate interleukin-6 in patients with cancer-associated anorexia and weight loss? A North Central Cancer Treatment Group investigation," Support. Care Cancer, 2002, doi: 10.1007/s00520-001-0310-7.

[13] T. E. Johnson, R. R. Casiano, J. W. Kronish, D. J. Tse, M. Meldrum, and W. Chang, "Sino-orbital aspergillosis in acquired immunodeficiency syndrome," Arch. Ophthalmol., 1999, doi: 10.1001/archopht.117.1.57.