

Case Study

DOI: 10.29011/2575-9760.001161

The Role of Novel Phyto-Cannabinoids and their Immuno-Synergistic Effects in Heart Transplantation: A 6 Year Case Study

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Citation: Wetherell ND, Bates MJ, Frye LN (2018) The Role of Novel Phyto-Cannabinoids and their Immuno-Synergistic Effects in Heart Transplantation: A 6 Year Case Study. J Surg: JSUR-1161. DOI: 10.29011/2575-9760.001161

Received Date: 01 August, 2018; **Accepted Date:** 31 August, 2018; **Published Date:** 07 September, 2018

Introduction

Cardiac transplantation has long presented the problem of requiring lifelong immune suppression for adequate maintenance of the allograft organ. Major, lifelong, and terminal ailments and diseases arise from the use of these immune suppressing medications. For Transplant patients, the immune system's Human Leukocyte Antigens function is suppressed to prevent rejection of the allograft [1-4]. Immunosuppressant medications cause the immune system to become less effective at its primary job of protecting the patient from infections and certain types of cancer [1,5]. Immune suppressants can be divided into their respective classes. The calcineurin inhibitors govern the action of cytotoxic lymphocytes, anti-proliferative agents directly inhibit the proliferation of T and B lymphocytes, and the mTOR inhibitors inhibits T-cell proliferation and proliferative responses induced by several cytokines, including interleukin 1s through 6. [1,2,5-7]. Steroids are standard immune suppression therapy for organ transplantations as well as an anti-inflammatory agent. These medications have been shown in clinical trials to increase the chance of the recipient developing cancer [6,7]. Drugs from these classes, such as Tacrolimus, Mycophenolate Mofetil, and Prednisone are the standard form of immune suppression following cardiac transplant [7]. Immune suppression is one of the leading causes of death for transplant recipients due to complication such as infection, cancer, kidney failure, liver failure and failure of the

allograft [1,2]. These medications can also increase the risk of developing other chronic diseases in transplant recipients, such as diabetes [1,2,6]. This article examines the use of naturally occurring plant based pharmacological properties of cannabis sativa, known as Phyto-cannabinoids, for immunological use in heart transplantation.

Methods

This paper is a case study of a cardiac transplant recipient 6 years post transplantation and the effects of novel Phyto-cannabinoids in the course of the patient's treatment. We also investigate the role of Endogenous Cannabinoids and the function of the Endogenous Cannabinoid System and its role in regulating the Major Histocompatibility Complex and the Human Leukocyte Antigen response in organ transplantation. We are investigating novel Phyto-cannabinoids as a means of immune suppression. Six months post-transplant the patient began using various cannabis products for pain suppression, nausea control, in appetite and opioid dependence and opioid withdrawal. At 11 months following transplant the Allomap test (XDX Corp. Gene-Assay) was used as a non-invasive method for monitoring the patient for cardiac allograft rejection. The Allomap gene assay test results were compared to Tacrolimus dose and the type cannabinoid therapy used at that time (Table 1).

Date of Draw	TAC Dose 2X Daily	Tacrolimus Level Range 5.0-20.0	Allomap Score 0-40	+/- from previous test	+/- from BASE	Cannabinoid Therapy Used
Apr-13	8mg	10.4	30	(BASE)	30 (BASE)	None
Jul-13	8mg	14.3	26	-4	-4	CBD Tincture
Aug-13	5mg	8	24	-2	-6	Dronabinol, cannabis s. NLD Tinc.
Jun-14	3mg	10.1	24	0	-6	Dronabinol, cannabis s. NLD Tinc.
Oct-14	2mg	14.5	28	4	-2	Dronabinol only
May-15	2mg	7.9	21	-7	-9	CBD tincture, Marinol, cannabis s. NLD Tinc.
Jun-16	2mg	5.9	32	11	2	None
May-17	2mg	10.9	26	-6	-4	Cannabis S. NLD Tinc. CBD Tinc.
Jun-18	2mg	7.1	29	3	-1	Dronabinol only

Table 1: Allomap Assay Results with Cannabinoid Chart.

The patient is a 25-year-old male with prior history of end stage, non-ischemic cardiomyopathy secondary congenital heart disease (pulmonic stenosis, Atrial Septal Defect and mitral valve prolapse status post Mitral Valve repair). A Heartmate II Left Ventricular Assist Device was implanted in 1/2012 followed by pump exchange in 3/2012 due to thrombosis. He was listed 1A at the time of transplant due to a pump pocket infection and underwent a successful heart transplant in May of 2012.

Results

Patient's symptoms, gait and appearance improved with use of cannabis products, symptoms including rapid opioid withdrawal at an amount of 80mg MS Contin twice daily, 35ml Methadone twice daily to no opioid use in 2 weeks, in contrast to the six months of failed opioid withdrawal requiring multiple hospitalization. Cannabis as a form of pain control was effective in this patient. The use of cannabinoids for pain control was more effective than opioids, and the risk of over dose was eliminated [8]. The patient's withdrawal symptoms were also minimal to nonexistent. Patient experienced an increase in appetite and gained body mass that was lost post LVAD infarcts and *C. difficile*. Patients appetite increased dramatically with the use of Cannabinoids as opposed to dronabinol

[9]. Patient also experienced a regulation in blood glucose levels from 300+ too below 120 and maintained normal glucose level resulting in their diabetes to alleviate. But most intriguing was the rapid reduction of Allomap immune assay results in association with certain cannabinoids and mean of ingestion, as documented in the above chart. Also noted was a dramatic decrease in anti-rejection medication from 10mg prednisone twice daily to NONE, 8 mg tacrolimus to 2 mg twice daily with tacrolimus serum levels

remaining therapeutic, 2500mg mycophenolate twice daily to 500mg Twice daily while still maintaining therapeutic dosing. In the six years since transplantation the patient did not experience any acute or chronic rejection of the graft nor any major infections.

The patient was able to maintain adequate tacrolimus blood serum levels of immune suppression while concurrently increasing cannabis consumption and decreasing need for immune suppression. Tacrolimus and Mycophenolate doses were decreased and Prednisone was discontinued. The above chart indicates that there was no significant increase or decrease of Tacrolimus serum in the patient's blood, in relation to cannabinoids present in the blood stream, nor is there any direct effect on Tacrolimus levels relating to which method of ingestion occurs.

Discussion

In 1905 Alexis Carrel a French biologist and surgeon began transplanting puppy hearts into the necks of adult canine animals [5]. In the 1950s and 1960s Shumway and his team at Stanford University began using extracorporeal preservation utilizing local hypothermia induction directly to the cardiac muscle of canines for investigation into the future possibility of homograft transplantation [5,10]. After several more physiological breakthroughs such as attaining viable surgical anastomosis between the graft and the host, the denervation of the cardiac muscle while still maintaining viability and the use of the new heart/lung bypass machine, many of the previous physiological objections to transplantation were silenced [2]. By 1963 canine cardiac transplants proved physiologically possible [2]. The transplant community was ready to begin human trials, but the one major remaining hurdle was the need for aggressive investigations surrounding the histological

response of the Human Leukocyte Antigens [11,12]. The major issues surrounding the transfer of cardiac tissue from one Patient to another was the major histocompatibility complex and the issue of acute and chronic rejection of the tissue [2]. By 1965, Shumway and his team were able to overcome almost every major obstacle in cardiac transplantation except the issue surrounding graft rejection by the recipient. In the early days of renal graft transplantation, it was mainly performed between twins, total body irradiation was used and the donor organ and bone marrow were implanted at the same time [5]. This process proved dangerous and lethal [5].

In 1976 Sandroz, Stahelin et al. isolated the chemical structure of cyclosporine. It was discovered that cyclosporine was a powerful drug for many new medical applications [6]. In the 1980s It was shown that Cyclosporine in combination with other immune suppressing drugs greatly increased the likely hood of Patient survival post-transplant [6,10]. The biopsy of the myocardium of the right ventricle is the standard for testing for acute organ rejection within the graft [10,13,14]. This procedure is performed under sterile conditions using Right heart catheterization technique to retrieve tissue sample for biopsy of the right ventricle. Usually 5 samples are retrieved and placed in solution to be sent to a laboratory for analysis to detect if there is any sign of cardiac rejection [14,15]. The AlloMap test is a noninvasive test that quantifies intracellular mRNA levels in mononuclear cells in peripheral blood samples using real-time polymerase chain reaction; this test has been shown to distinguish the dynamic changes in gene expression that occur in the presence or absence of acute cellular rejection [13]. AlloMap test was clinically validated in the Cardiac Allograft Rejection Gene Expression Observational study, in which an 11-gene real-time PCR test prospectively distinguished quiescence from biopsy-proven moderate-severe rejection in 63 asymptomatic patients (t test, $P = .0018$) [13]. In the study, a score below 30 had a negative predictive value of 99.6% for patients more than 1 year after transplantation, suggesting that the AlloMap might be an alternative to biopsy to rule out rejection in a lower-risk population [13].

Dr. Melchoulam isolated a Phyto-cannabinoid from the resin of the cannabis plant. This was the discovery of DELTA-9-THC [16]. In 1992 Raphael Mechoulam at Hebrew University discovered and isolated the first Endogenous Cannabinoid and named it Anandamide, (Ananda) after the Sanskrit word for Bliss. At the same time, researchers Robert Devane and Dr. Lumir Hanus at Washington University, St. Louis, Missouri, USA discovered the first Endogenous Cannabinoid receptors in rat brains which then led to the discovery of the Endogenous Cannabinoid System, or ECS [17]. This discovery led to the synthesis and use of DELTA-9-THC, Dronabinol name brand Marinol, to treat wasting syndrome and nausea following chemotherapy treatment for malignant growth. It has been shown that the human cardiac muscle expresses an abundant amount of CB1/2 receptors,

making it susceptible to CB1 agonist/antagonist activation, and in addition, other receptors not yet identified and isolated [18]. The cardiac muscles expression of these receptors are important in maintaining the hearts physiological function, homeostasis, and protects the organ from ischemia related injuries [19-23]. The effects of CBDs anti-plaque and anti-protein properties have the ability to help prevent atherosclerosis or the hardening of arterial walls and buildup of plaque [24-26]. Along with CBDs proven ability to reduce inflammation including in the cardiac muscle and surrounding vessels [24,25] it has potential to be a potent immunosuppressant medication by reducing the T-cell storm in cardiac transplantation [19,21-23,27-29]. The hearts expression of CB1 and CB2 receptors presents an interesting intersection of effects cannabinoids and their respective agonistic responses to their respective receptors cardiological effects. In the case of the cardiac Endogenous Cannabinoid System, CB1 and CB2 receptors seem to play opposing roles against each other [18,26,29]. This would explain the effects of certain cannabinoids like, THC on blood pressure and heart rate, but not similar effects from other cannabinoids such as CBD [18,19, 22,24,25]. CBD has also been shown to be a Novel cannabinoid with the effect of being a potent anti-inflammatory [30,31]. The presence of cannabinoid receptors in the cardiac muscle also increases cannabinoids effects on the muscle such as an anti-inflammatory and anti-HLA properties similar to ones experienced in cases where cannabinoids have been used to induce Apoptosis in cancerous, tumorous growths [18,23,32-34].

The activation of CB2 receptors in cardiac models has shown a protective effect on the cardiac muscle after reperfusion following ischemia time [35]. This shows that activation of the CB2 receptor can protect the cardiac muscle from cellular injury or death from Ischemia following an infarct [35]. *In vivo* studies showed the infarct size was significantly reduced in CBD-treated rat hearts as determined after 7 days, together with reduced myocardial inflammation and improved left ventricular function [25,26]. This is of course using the lesser known, non-psychoactive Cannabidiol or CBD [19,22,24-26]. By using inhaled Phyto-cannabinoids, the uptake of THC and CBD into the blood stream is much greater and more profound. Maximum drug efficiency plateaus at about 4-7 minutes after initial inhalation. Because the cannabinoids don't pass through the liver, as they do for edible cannabis, thus reducing the effects of the CYP3YA Enzymes, which deactivate cannabinoids before entering the blood stream [36,37]. This is also a more beneficial way to intake cannabinoids and retain them in the brain as a means of protection from neurological ischemic damage in the event of a cerebral vascular accident/infarct. THC has been shown to be a potent neuroprotectant [38]. It was discussed that selectiveness of liver enzymes could have an affinity for certain chemical constituents and the liver could be selecting cannabinoids over Tacrolimus.

Conclusion

In conclusion, in this patients case using cannabinoids in conjunction with immune suppressing drug therapy suppress' the HLA rejection, including but not limited to decreasing the endothelial cell activation/inflammatory response (for example, expression of adhesion molecules, secretion of chemokines, and so on), and by attenuating the leukocyte chemotaxis, rolling, adhesion to endothelium, activation and trans endothelial migration, and interrelated oxidative/nitrosative damage [3,25,30,31]. As can be seen in studies done on rats, it appears that cannabis does not suppress the immune system but rather induces immune modulating effects. It has been shown that Phyto-cannabinoids decrease Th1 Cytokines, increases Th2 Cytokines, down regulates mast cell activity and possibly neutrophils [3,27,29,39].

The results shown above indicate that not only are Phyto-cannabinoids beneficial in producing a desired immune-modulating effect, but artificially created cannabinoids such as Dronabinol also play a therapeutic role in control of cardiac transplant rejection. There was no evidence of the liver being cannabinoid selective over tacrolimus. Cyclosporine, tacrolimus, CBD, CBDA, CBN, DELTA9THC, THCa, Delta8THC, THCV, CBG [26] are all metabolized by the Cytochrome PY4503y4 enzyme which could also help explain the reduced amount of immune suppression via pharmacological intervention [40-42]. With the previously stated studies and models of research presented and this Patients outcome presented as a body of evidence, much more research into this particular route of immune suppression/synergism is needed in both clinical and academic environments.

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