CHRONIC PAIN TREATMENT WITH CANNABIDIOL IN KIDNEY TRANSPLANT PATIENTS IN URUGUAY

Leticia Cuñetti, Raquel Peyraube, Laura Manzo, Lilian Curi, Sergio Orihuela. Nephrology and Urology Institute, Kidney Transplant Unit. Uruguay.

Introduction

Chronic pain is a major therapeutic problem in kidney transplant patients due to the limitation of using NSAID because its nephrotoxicity.
There is benefit of the modulation of the eCS in the treatment of chronic pain.
Our main concern was the potential drug interactions between CBD and calcineurin inhibitors as both are metabolized by CYP.
Furthermore CBD can act as an inductor or an inhibitor of CYP.
The use of cannabidiol (CBD) in kidney transplant patients has not been communicated previously.
Kidney transplantation is the gold standard for renal function replacement in patients with extreme chronic kidney disease. Immunesuppression to avoid graft rejection has been evolving over the years.
However, there have been no major advances since the introduction of cyclosporine in the 1980s.
Immune tolerance is the goal of immunesuppression in solid organ transplantation, defined as the state of non-response to the alloantigens present in the graft while maintaining an adequate immune response to other stimuli.
Kidney tranplant patients with adequate levels of immunesuppression to avoid graft rejection are at a higher risk of infections and cancer as its main complications.
Anandamide induces bone marrow derived dendritic cell apoptosis through CB1 and CB2 receptor, inhibiting antigen presentation to CD4 lymphocyte inhibiting Th1 and Th17 response.
Also it inhibits T lymphocyte proliferation, it's migration and activation, IL-2 secretion, and promotes its apoptosis.
Cannabinoids have 3 main effects in cancer:
1.Induction of cancer cell apoptosis and inhibition of proliferation by increasing ER stress and autophagy
2. Inhibition of angiogenic signals by inhibition of VEGF pathway.
3. Inhibition of adhesion, migration and invasion by inhibiting MMP2
Since all the above, our hypothesis is that CBD administration could be protective for this patients:
- reducing the incidence of graft rejection (alone or added to immunesuppression treatment)
- reducing the incedence of cancer
- releaving pain without significant risks for this patients.

Objective: **We aimed to assess the effect, safety and potential drug interactions in kidney transplant patients treated with CBD for chronic pain.**

Methods: We assessed patients who asked for CBD treatment for uncontrolled chronic pain. They receive progressive doses from 50 mg to 150 mg twice a day for 3 weeks of CBD. Weekly medical visits where we determine creatinine, blood count, functional and liver enzyme and drug levels.

Results: **We assessed 7 patients (table 1)** Initial dose of CBD was 100 mg/day, CBD dose reduction to 50mg/day has been done on day 4 in patient n°1 due to persisting nausea. Tacrolimus dose reduction in patient nº3 has been done in day 4 and 7 due to persisting elevated levels (before CBD) and itching and in day 21 in patient n°5. Tacrolimus levels decreased in patient n°2 but were normal in the control one week later. Patients in cyclosporine were stable. Adverse effects were nausea, dry mouth, dizziness, drowsiness and episodes of intermittent heat, which required CBD dose decrease in 2 patients.2 patients had total pain improvement, 4 had a partial response in the first 15 days and in one there was no change

Table1. Base line characteristics and results in day 1 and 21 per patient

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient7	
Age	75		58		61		60		60		73		65	
Sex	F		M		F		M		M		F		M	
Pain Cause	Fibromyalgia		Osteoarticular		Fibromyalgia		Osteoarticular		Osteoarticular		Osteoarticular		Neuropathic	
Day	1	21	1	21	1	21	1	21	1	21	1	21	1	21
Creatinine mg/dl	1.10	1.04	1.03	1.12	0.92	0.89	1.14	1.16	1.94	2.8	2.07	1.95	2.39	2.36
Hemoglobin g/dl	11.4	10.7	13.4	13.1	12.4	12.9	15	14.3	11	10.2	11.5	10.9	14.7	14.8
Leucocytes mm3	3990	4370	7080	8960	4480	5280	8830	10850	7420	6360	12900	11760	10100	126oo
Platelets(10^3 m3)	185	174	215	237	182	199	248	245	189	174	306	265	157	213
TGO/TGP (mg/dl)	14/11	14/10	14/18	16/22	20/12	19/12	16/9	12/8	16/11	15/11	25/19	19/16	19/16	16/19
Tacrolimus (ng/ml)	10.1	6.5	7.4	2.8	14.4	16.7	9.7	9.8	7.8	13.8	-----	-----	-----	-----
Cyclosporine (ng/ml)	----	----	----	----	----	----	----	----	----	----	355	332	261	291

Pain Score Index (1-10) / Limitation perception (none, mild, moderate, severe)

Patient	week -1	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14	Day 21
1	6/moderate	5/moderate	5/moderate	5/mild	2/mild	2/mild	2/mild	3/mild
2	2/mild	2/none	2/none	2/none	2/none	2/none	2/none	2/none
3	4/mild	1/none	1/none	1/none	3/mild	3/none	4/none	2/none
4	7/moderate	4/mild	4/mild	4/mild	4/mild	3/mild	4/mild	3/mild
5	7/moderate	6/moderate	4/mild	4/mild	4/mild	4/mild	8/severe	6/moderate
6	7/moderate	6/moderate	3/mild	2/none	2/none	0/none	0/none	0/none
7	9/severe	8/severe	4/mild	2/mild	2/none	2/none	2/none	2/none

Conclusion: During this period of follow up, CBD was well tolerated and we didn't find any severe adverse effect.
Tacrolimus plasma levels had a variability that requires longer follow up to assess possible drug interactions. In the 2 patients with cyclosporine, plasma levels were steady. There is need to follow up more patients. Meanwhile we recommend weekly calcineurin inhibitors determinations during the first month of CBD treatment followed by monthly determination of calcineurin inhibitors..