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Optic neuropathy after long-term treatment with tacrolimus — a case series

ABSTRACT

Introduction. Optic neuropathy is a rare but severe complication of tacrolimus treatment. We present a case series of 4 patients with optic neuropathy after long-term tacrolimus therapy who underwent organ transplantation.

Material and methods. The study included 4 patients (8 eyes) who were diagnosed with optic neuropathy in the course of tacrolimus treatment conducted due to a kidney transplant (3 patients) and a liver transplant (1 patient). Each patient underwent an ophthalmic examination (best corrected visual acuity test, applanation tonometry, slit-lamp examination, visual field test) at the time of visual acuity decline and half a year afterward. Additionally, at the second examination, spectral-domain optical coherence tomography (SD-OCT), evaluating the retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer complex (GCL-IPL), was performed.

Results. During the first examination, the anterior segment and fundus were unremarkable except for papilledema in the affected eye. Visual acuity, half a year after the onset of neuropathy, was close to the initial state. Intraocular pressure remained stable during the entire time of follow-up. In the perimetric examination, the neuropathy-affected eye was characterized by concentric narrowing of the visual field during the whole follow-up period. On SD-OCT, in all examined patients, we observed a persistent statistically significant decline in the mean thickness of the RNFL and GCL-IPL. In the case of the RNFL (around the optic disc), injury to superior and inferior sectors prevailed.

Conclusion. Tacrolimus-associated optic neuropathy can be observed years after transplantation and with the absence of toxic blood levels. SD-OCT is a quick and non-invasive method of tacrolimus-associated optic neuropathy assessment.

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INTRODUCTION

Calcineurin inhibitors (including tacrolimus) are immunomodulating and anti-inflammatory agents. By inhibiting calcineurin activity, which works in cells as an element of a signaling pathway leading to T cell activation, calcineurin inhibitors impede the transcription of inflammatory cytokines. They are commonly used in transplantology, as well as in dermatology (e.g. Protopic). Tacrolimus (FK-506) was discovered in 1984 in Japan. It is a macrolide antibiotic produced by Streptomyces tsukubaensis. It is believed that its immunosuppressive activity is a hundred times stronger than cyclosporine As. The immunosuppressive mechanism of FK-506 is based on binding to immunophilin (FKBP12), inhibiting Ca-dependent signaling cascades in T lymphocytes. Due to this fact, tacrolimus prevents synthesis of interleukins, such as IL-2, IL-3, IL-4, IL-5, and other cytokines, such as granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-alpha, and interferon gamma. Tacrolimus also hinders release of mediators of inflammation from mast cells, basophils, and eosinophils. Compared to cyclosporine A, the drug shows less nephrotoxic effect [1, 2].

Optic neuropathy is a rare, but severe complication of FK-506 treatment. Several

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cases of tacrolimus-associated optic neuropathy in organ transplant patients have been reported in the literature and concerned patients after liver, small bowel, pancreatic islet cell, pancreas, heart, and kidney transplantations [3–9]. Ocular symptoms and examination findings were significantly asymmetric in two of these cases [3, 7]. The interval between tacrolimus therapy initiation and symptom onset ranged from three months [3, 9] to five years [7]. In the majority of the reported cases, the absence of toxic blood levels of tacrolimus was observed [4–7, 9]. Cessation of tacrolimus therapy may not necessarily result in an improvement of visual acuity; the risks of drug discontinuation and expected benefits should be weighed [8].

MATERIAL AND METHODS

In this study, we included 4 patients (8 eyes), 1 woman and 3 men, who were diagnosed with optic neuropathy in the course of tacrolimus treatment. All patients were consulted by an ophthalmologist due to acute painless narrowing of the visual field in one (2 patients) or both eyes (2 patients). The mean age of the patients was 40.5 ± 19.6 years old (range 19–59 years old). The mean age at the optic neuropathy onset was 45.0 ± 17.4 years old (range 27–64 years old). Immunosuppressive therapy was conducted owing to a kidney transplant (3 patients) and a liver transplant (1 person). The patient characteristics are presented in Table 1.

Each patient underwent ophthalmic examination twice: 1) at the time of a sudden visual acuity decline and 2) half a year after the decline. Between our control examinations, the patients were under local ophthalmologist care. The ophthalmic examination involved: the best corrected visual acuity test using the Snellen Chart, applanation tonometry, slit-lamp examination, and visual field test (Humphrey visual field analyzer). Additionally, half a year following the decline in visual acuity, spectral-domain optical coherence tomography (SD-OCT) was performed.

Spectral-domain optical coherence tomography scanning was conducted with 3D SOCT 2000 (Topcon Corporation 75-1, Hasunuma-cho, Itabashi-ku, Tokyo 174-8580, Japan). The device is characterized by 5-6 μm in-depth resolution, 2.3 mm penetration depth, 50000 A-scans per second (acquisition speed), and 580 nm center wavelength. We chose this device because of the convenience and speed of scanning, its ability to generate a fundus image for each scan, its ability to analyze the retinal nerve fiber layer (RNFL), ganglion cell-inner plexiform layer complex (GCL-IPL,) and its accurate macular scans. In addition, this equipment allows one to generate 3D images, hence the scanned image can be viewed in three dimensions. SD-OCT evaluated parameters such as foveal retinal thickness, macular morphology, RNFL thickness (in the region of the optic nerve — 'disc scan' and the area of the macula — 'macula V' scan), and the GCL-IPL complex thickness — 'macula V' scan. Retinal layers were estimated as follows: the RNFL: from the inner limiting membrane to the RNFL/GCL and the GCL-IPL: from the RNFL/GCL to the IPL/inner nuclear layer. The manufacturer's normative reference database was used in the evaluation of our results. Because of the emergence of cataracts in a female patient, we excluded her results from the analysis.

All statistical calculations were done with DELL INC. software (2016) Dell Statistica (data analysis software system), version 13 (software.dell.com), and the Excel spreadsheet. The significance of differences between two groups was evaluated by Student's t-test and Mann-Whitney U test. The chi-Square test of independence was used for qualitative variables. In all performed calculations, the significance level was set at $p = 0.05$.

RESULTS

In the first examination, the anterior segment of the eye was unremarkable. The macula and the retina remained unchanged. The only pathological sign was papilledema in the affected eye (Fig. 1).

In the perimetric examination, we observed concentric narrowing of the visual field.

One of the patients underwent a supplemental visual evoked potential (VEP) test, which demonstrated prolonged latency and a decrease in P100 amplitude corresponding to demyelination and axonal injury of the optic tract.

VISUAL ACUITY

The mean visual acuity of the right eye at the time of vision worsening was 0.7 (0.5) and in the examination half a year later was 0.7 (0.4). No statistically significant difference was found in the right eye visual acuity change ($p = 0.6547$).

Table 1. The patient characteristics

Case	Age at onset of ON	Sex	Type of Tx organ	Date of Tx	Onset of ON	Immunosuppressive treatment	Intervention
1	55	F	K	2008-03-13	2013	S, MMF, TAC	None
2	34	M	K	2012-12-06	2017	S, MMF, TAC	Conversion to EVR
3	27	M	K	2004-09-19	2012	S, MMF, TAC	Lowering of TAC dose
4	63	M	L	2013-02-15	2017	S, MMF, TAC	None

EVR — everolimus; F — female; K — kidney; L — liver; M — male; MMF — mycophenolate mofetil; ON — optic neuropathy; S — steroids; TAC — tacrolimus; Tx — transplantation

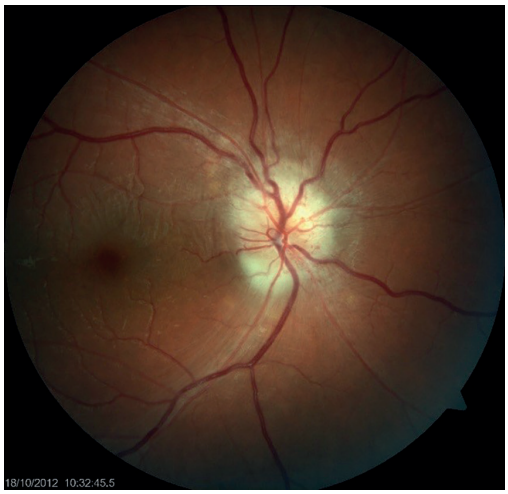

Figure 1. Papilledema of the right eye of a patient after a kidney transplant treated with tacrolimus

The mean visual acuity of the left eye in the initial examination was 0.7 (0.4), while half a year later it was 0.6 (0.4). No statistically significant difference was found in the left eye visual acuity change ($p = 0.6547$) (Tab. 2).

INTRAOCULAR PRESSURE

The mean intraocular pressure of the right eye during the first assessment was 16.0 (3.6) (range 11–19), and during the second was 13.8 (2.8) (range 11–17). No statistically significant difference was found in the right eye pressure change ($p = 0.2012$). The mean intraocular pressure of the left eye during the first assessment was 16.0 (5.4), and in the second was 15.0 (1.4) (range 13–16). No statistically significant difference was found in the left eye pressure change ($p = 0.5839$) (Tab. 3).

VISUAL FIELD

The percentage of patients with visual field narrowing in the right and left eyes was equal to 100% and 50%, respectively. However, 50% of examined patients presented with a narrowing of the visual field in both eyes.

RNFL AROUND THE OPTIC NERVE HEAD

In the examined group, the loss of the RNFL around the optic disc was found in 100% of patients in the inferior and superior segments of the right eye. In the case of the left eye, however, in 33.3% of patients, we found the loss in the inferior and superior segments (Tab. 4).

MACULAR RNFL

The percentage of patients who were affected by RNFL loss of in the examined group was 66.7% in both the inferior and superior segments of the right eye. Instead, in the left eye, the percentage of the loss in the inferior and superior segments was 33.3% each (Tab. 5).

MACULAR GCL-IPL COMPLEX

The percentage of patients with the loss within the GLC-IPL was 66.7% in the superior segment and 100.0% in the inferior segment of the right eye. In the left eye, however, the percentage of loss in both the inferior and superior segments was 33.3% (Tab. 6).

In order to determine the cause of optic neuropathy, diagnostic imaging — computed tomography and magnetic resonance imaging, and laboratory tests (for bacterial, viral, parasitic, and immunological diseases) — were performed.

Detailed medical history did not reveal any other comorbidities or therapies that could result in optic nerve injury. In all patients, tacrolimus blood trough concentrations (C_0) were within the therapeutic range (5–9 μg/L). Only in patient 3, the C_0/D ratio (calculated by dividing C_0 by the daily tacrolimus dose [D]) was 0.72 μg/L/mg and could be associated with greater toxicity.

Due to ophthalmic complications, in some patients, their immunosuppressive treatment was modified. In Patient 2 with stable kidney graft function, Prograf was withdrawn and an mTOR inhibitor (everolimus) was introduced.

Table 2. Characteristics of the examined group in terms of visual acuity

	First examination	Second examination	*P*-value
OD			0.6547
Mean (SD)	0.7 (0.5)	0.7 (0.4)	
Range	0.0–1.0	0.1–1.0	
Median	1.0	0.8	
95% CI	[0.0; 1.5]	[0.0; 1.3]	
OS			0.6547
Mean (SD)	0.7 (0.4)	0.6 (0.4)	
Range	0.0-0.9	0.0-0.9	
Median	0.9	0.7	
95% CI	[0.0; 1.3]	[–0.1; 1.2]	

CI — confidence interval; OD — right eye; OS — left eye; SD — standard deviation

Table 3. Characteristics of the examined group in terms of intraocular pressure

	First examination	Second examination	*P*-value
OD			0.2012
Mean (SD)	16.0 (3.6)	13.8 (2.8)	
Range	11.0–19.0	11.0–17.0	
Median	17.0	13.5	
95% CI	[10.3;21.7]	[9.4;18.1]	
OS			0.5839
Mean (SD)	16.0 (5.4)	15.0 (1.4)	
Range	11.0–22.0	13.0–16.0	
Median	15.5	15.5	
95% CI	[7.5; 24.5]	[12.7; 17.3]	

CI — confidence interval; OD — right eye; OS — left eye; SD — standard deviation

Table 4. Characteristics of the examined group in terms of nerve fiber (RNFL) loss around the optic disc

	The examined group (n = 3)
OD	
Inferior	3 (100.0%)
Upper	3 (100.0%)
Temporal	1 (33.3%)
Nasal	0 (0.0%)
OS	
Inferior	1 (33.3%)
Superior	1 (33.3%)
Temporal	0 (0.0%)
Nasal	0 (0.0%)

OD — right eye; OS — left eye

Table 5. Characteristics of the examined group in terms of nerve fiber (RNFL) loss of in the macula

	The examined group (n = 3)
OD	
Inferior	2 (66.7%)
Superior	2 (66.7%)
OS	
Inferior	1 (33.3%)
Superior	1 (33.3%)

OD — right eye; OS — left eye

Table 6. Characteristics of the examined group in terms of GCL-IPL loss in the macula

	The examined group (n = 3)
OD	
Inferior	3 (100.0%)
Superior	2 (66.7%)
OS	
Inferior	1 (33.3%)
Superior	1 (33.3%)

OD — right eye; OS — left eye

In Patient 3 Advagraf was changed into Prograf (formulation with a shorter half-life), and the daily dose was reduced by 1 mg to increase the C_0/D ratio and diminish drug toxicity exposure. Conversion to cyclosporine or mammalian target of rapamycin (mTOR) inhibitor was not performed due to signs of humoral rejection in the graft biopsy performed one year earlier and the risk of further decline in graft function. In the remaining patients, the immunosuppressive treatment was not modified, and low doses of Prograf were maintained.

DISCUSSION

The pathomechanism of tacrolimus toxicity on the optic nerve is not clear. A vascular mechanism involving the prostacyclin-thromboxane pathway, resulting in vasoconstriction has been postulated [3]. Fluorescein angiography findings — absolutely no blood flow in the optic discs in one report [6] and significantly delayed and reduced blood filling of optic discs in another [9] corroborate the hypothesis about the vasoconstriction mechanism of tacrolimus leading to ischemia. Venneti et al. [7] reported the results of an optic nerve biopsy performed in a patient with asymmetric bi-

lateral optic neuropathy associated with tacrolimus therapy, which led to severe vision loss (no light perception in one eye and hand movement in another). Microscopic findings showed a prominent loss of myelin in the optic nerve and the absence of significant vascular changes. Therefore, the author indicated oligodendroglial cell damage as a possible mechanism of tacrolimus toxicity and a possible reason for persistent vision loss after tacrolimus therapy cessation.

Furthermore, there is evidence that a polymorphism of genes coding ABCB1 protein, which constitutes a drug transporter in epithelial cells, might have an impact on tacrolimus elimination from the central nervous system (CNS). Patients characterized with such polymorphism can be more liable to the toxic effect of the drug on the CNS [10, 11].

In our study, half a year after the onset of neuropathy, visual acuity was close to initial values. Even if there was any improvement in vision, it was unremarkable. Intraocular pressure remained stable during the entire follow-up period. In perimetric testing, the eye affected by neuropathy presented with a concentric narrowing of the visual field throughout the whole period of observation.

After half a year of SD-OCT follow-up, we found a persistent, statistically significant decrease in the mean thickness of the RNFL and GCL-IPL in all examined patients. In the case of the RNFL (around the optic disc), injury of the superior and inferior segments prevailed.

Tacrolimus plays a crucial role in maintaining function of transplanted organs. Due to its narrow therapeutic index, as well as high interpatient and intrapatient pharmacokinetic variability, the management with tacrolimus requires individual dose adjustment to achieve therapeutic range and avoid under- and overexposure. However, regardless of maintaining target C_0 concentrations, patients requiring higher daily doses of tacrolimus (C_0 /D < 1.05 μg/L/mg) may experience a greater incidence of drug-related adverse events [12].

In the medical literature, there are descriptions of cases of vision improvement after cessation of tacrolimus treatment [5, 6, 9]. To avoid conversion to another calcineurin inhibitor, cyclosporin or mTOR inhibitors may be considered. However, everolimus-induced posterior reversible encephalopathy syndrome and optic neuropathy in a patient after kidney transplantation was reported [13].

A decision about reduction, discontinuation, and conversion of tacrolimus treatment should be cautious and take into account the risk of deterioration or even loss of the functioning transplant as well as possible benefits [14].

SUMMARY

Tacrolimus-associated optic neuropathy could be observed years after transplantation and cannot be explained by toxic blood levels. On SD-OCT, we found a persistent, statistically significant decrease in the mean thickness of the RNFL and GCL in all examined patients. In the case of the RNFL (around the optic disc), there was a prevalence of injury of the superior and inferior segments. SD-OCT is a quick and non-invasive method of optic neuropathy assessment.

GRANT INFORMATION

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CONFLICT OF INTEREST

None to declared.

References

1. Danysz A. Kompendium farmakologii i farmakoterapii. Urban&Partner, Wrocław 2004: 236.
2. Hatanaka H, Kino T, Miyata S, et al. FK-506, a novel immunosuppressant isolated from a Streptomyces. I. Fermentation, isolation, and physico-chemical and biological characteristics. J Antibiot (Tokyo). 1987; 40(9): 1249–1255, doi: 10.7164/antibiotics.40.1249, indexed in Pubmed: 2445721.
3. Brazis PW, Spivey JR, Bolling JP, et al. A case of bilateral optic neuropathy in a patient on tacrolimus (FK506) therapy after liver transplantation. Am J Ophthalmol. 2000; 129(4): 536–538, doi: 10.1016/s0002-9394(99)00443-2, indexed in Pubmed: 10764869.
4. Lake DB, Poole TRG. Tacrolimus. Br J Ophthalmol. 2003; 87(1): 121–122, doi: 10.1136/bjo.87.1.121, indexed in Pubmed: 12488279.
5. Kessler L, Lucescu C, Pinget M, et al. GRAGIL. Tacrolimus-associated optic neuropathy after pancreatic islet transplantation using a sirolimus/tacrolimus immunosuppressive regimen. Transplantation. 2006; 81(4): 636–637, doi: 10.1097/01.tp.0000188946.82239.68, indexed in Pubmed: 16495816.

6. Yun J, Park KA, Oh SY. Bilateral ischemic optic neuropathy in a patient using tacrolimus (FK506) after liver transplantation. Transplantation. 2010; 89(12): 1541–1542, doi: 10.1097/TP.0b013e3181d2fe83, indexed in Pubmed: 20559109.
7. Venneti S, Moss HE, Levin MH, et al. Asymmetric bilateral demyelinating optic neuropathy from tacrolimus toxicity. J Neurol Sci. 2011; 301(1-2): 112–115, doi: 10.1016/j.jns.2010.10.014, indexed in Pubmed: 21112060.
8. Ascaso FJ, Mateo J, Huerva V, et al. Unilateral tacrolimus-associated optic neuropathy after liver transplantation. Cutan Ocul Toxicol. 2012; 31(2): 167–170, doi: 10.3109/15569527.2011.629325, indexed in Pubmed: 22035458.
9. Shao X, He Z, Tang L, et al. Tacrolimus-associated ischemic optic neuropathy and posterior reversible encephalopathy syndrome after small bowel transplantation. Transplantation. 2012; 94(9): e58–e60, doi: 10.1097/TP.0b013e31826dde21, indexed in Pubmed: 23128973.
10. Arceci RJ, Stieglitz K, Bierer BE. Immunosuppressants FK506 and rapamycin function as reversal agents of the multidrug resistance phenotype. Blood. 1992; 80(6): 1528–1536, doi: 10.1182/blood.v80.6.1528.bloodjournal8061528.
11. Yamauchi A, Ieiri I, Kataoka Y, et al. Neurotoxicity induced by tacrolimus after liver transplantation: relation to genetic polymorphisms of the ABCB1 (MDR1) gene. Transplantation. 2002; 74(4): 571–572, doi: 10.1097/00007890-200208270-00024, indexed in Pubmed: 12352921.
12. Brunet M, Pastor-Anglada M. Insights into the Pharmacogenetics of Tacrolimus Pharmacokinetics and Pharmacodynamics. Pharmaceutics. 2022; 14(9), doi: 10.3390/pharmaceutics14091755, indexed in Pubmed: 36145503.
13. Touhami S, Arzouk N, Darugar A, et al. Everolimus-induced posterior reversible encephalopathy syndrome and bilateral optic neuropathy after kidney transplantation. Transplantation. 2014; 98(12): e102–e104, doi: 10.1097/TP.0000000000000551, indexed in Pubmed: 25955341.
14. Rasool N, Boudreault K, Lessell S, et al. Tacrolimus Optic Neuropathy. J Neuroophthalmol. 2018; 38(2): 160–166, doi: 10.1097/WNO.0000000000000635, indexed in Pubmed: 29420328.