PALLIATIVE CARE
CASE OF THE MONTH

"Rage and Ramble, Shiver and Shake - Tacrolimus Neurotoxicity"

by
Justin Yu, MD

Volume 17, No. 78 **March 2017**

Case: DB is a 50- year-old male with a history of ischemic cardiomyopathy (s/p heart transplant one month prior to our evaluation), prior stroke and bipolar disorder. We were consulted for delirium. His post-operative course had been complicated by acute renal failure requiring hemodialysis. Since transplant, his team observed that his personality seemed persistently "off" from baseline. He was also noted to have intermittent visual hallucinations (conversations with no one in the room). Despite initiation of low-dose Zyprexa, his hallucinations became more frequent, and he became more irritable and agitated. The only notable exam finding was significant bilateral hand tremors (at rest, but worse with intention). Interestingly, he had insight to the fact that clinicians believed he was having hallucinations, though he denied experiencing them. He was not disoriented, confused, or forgetful. He occasionally stuttered and his speech content was slightly tangential. His immunosuppressive regimen consisted of tacrolimus, mycophenolate, and prednisone. He was also maintained on home medications of Lamictal and Zoloft for his bipolar disorder.

Discussion: Tacrolimus, also known as FK-506 or Prograf, is a macrolide antibiotic with immunosuppressive activity and belongs to the calcineurin inhibitor family (similar to cyclosporine). It was discovered in 1984 from a Japanese soil sample as a metabolite of the fungus Streptomyces tsukubaensis. The first human trials as a transplant medication occurred here at the Starzl Institute in 1989.[1] Tacrolimus works by binding to calcineurin and preventing its activation of T-cell production of IL-2 and other cytokines.[2] While primarily used for organ rejection prophylaxis after solid tumor transplant, it has also been used in the treatment of transplant rejection, autoimmune diseases, and atopic dermatitis.

Tacrolimus is associated with multiple, serious side effects including nephrotoxicity, hypertension, glucose intolerance, increased susceptibility to infection, and increased risk of malignancy (i.e., post-transplant lymphoproliferative disease). The most common symptomatic adverse reactions include GI upset, headache, and peripheral neuropathy.[3]

Over time, CNS neurotoxicity has become an increasingly recognized complication. While colloquially described as "patients who rage and ramble, shiver and shake" by transplant clinicians, tacrolimus' neurotoxicity is a spectrum of severity. The most common early side effect is tremor in the upper extremities which worsens with arms held in extension. If continued or even higher doses of tacrolimus are given, patients can progress to mental status changes, typically starting with restlessness, photophobia, and insomnia. If untreated, mania and psychosis with visual hallucinations and delusions can develop. During this time, speech will typically become distorted as well. At first rambling and slurred, patients can then develop stuttering (myoclonic speech), mutism, and speech apraxia (unable to protrude tongue or blow kisses). In the most severe stages of neurotoxicity, patients develop cortical blindness and confabulate regarding their environment. Lastly, the most severe side effects include seizures, status epilepticus and coma.[4, 5]

Reported incidences of tacrolimus-induced neurotoxicity vary widely, largely due to under-diagnosis. Adding to this ambiguity, the risk of neurotoxicity seems to differ with the type of organ being transplanted. There is broad agreement that patients who have undergone liver transplant are at the highest risk. Reported rates of neurotoxicity in lung, heart, and renal transplant vary considerably. Some degree of symptoms seems to develop in 20-30% of all patients on tacrolimus, with about 3-5% developing severe manifestations. Patients are most vulnerable in the acute post-operative period, especially if they have received large intravenous loading doses.[6, 7]

The pathophysiology of tacrolimus-induced neurotoxicity remains unclear. In-vitro studies have demonstrated dysregulation of NMDA and GABA receptors and alteration of CNS sympathetic output. Other investigations have shown all calcineurin inhibitors exhibit selective toxicity to glial cells and oligodendrocytes (i.e., white matter). Regardless, most researchers agree that the final common pathway is the development of vasogenic edema, which if allowed to persist, results in cytotoxicity.[4]

Diagnosis remains largely clinical. While MRI is useful for confirmation, the majority of patients with neurotoxic symptoms will not demonstrate significant findings and the prevalence of neuroimaging abnormalities is unknown. Though posterior leukoencephalopathy (in a pattern similar to PRES) is the most characteristic finding, white matter changes throughout the brain have been reported. Lastly, it is well documented that serum peak levels of tacrolimus are more predictive of neurotoxicity than trough levels.[4]

The first step of treatment is either dose reduction or ideally, discontinuation of tacrolimus. Interestingly, cessation of tacrolimus and changing to cyclosporine (also a calcineurin inhibitor) may result in resolution of symptoms. Another option is a time-limited replacement with Mycophenolate (Cellcept) and then restarting Tacrolimus at lower dose. There are numerous case reports about successful use of anti-psychotics in tacrolimus neurotoxicity; however, the evidence base remains anecdotal. Benzodiazepines are typically used for seizures.[5]

Resolution of Case: The differential for his delirium was broad and included metabolic disturbance, new stroke, non-convulsive seizures, infection, hypothyroidism, and medications. An MRI was not possible due to the presence of a pacemaker. It was felt that he would not cooperate with EEG. After ruling out other potential causes and worsening of his tremor with escalation of his tacrolimus regimen, we recommended that the transplant team consider stopping or decreasing the tacrolimus dose. The transplant team ultimately stopped and changed to cyclosporine. His tremors stopped within days, and his mental status returned to baseline. Zyprexa was stopped without issue.

References:

1. Klintmalm GB. FK 506: an update. Clin Transplant. 1994; 2:207-120.
2. Wiederrecht G, et al. The mechanism of action of FK-506 and cyclosporine A. Ann NY Acad Sci. 1993; 696 (9).
3. Fung JJ, et al. Adverse Effects Associated with Use of FK-506. Transplant Proc. 1991; 23(6): 3105-3108.
4. Wijdicks EF. Neurotoxicity of Immunosuppressive Drugs. Liver Transplantation. 2001; 7(11): 937-942.
5. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int. 2000; 12: 313-326.
6. Eidelman GH, et al. Neurologic complications of FK 506. Transplant Proc. 1991; 23: 3175-3178.
7. Mueller AR, et al. Neurotoxicity after orthotopic liver transplantation. A comparison between cyclosporine and FK 506. Transplantation. 1994; 58: 155-170.