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CONVERSION TO NEORAL FOR NEUROTOXICITY AFTER PRIMARY ADULT LIVER TRANSPLANTATION UNDER TACROLIMUS [1]

Jain, Ashok[2] [3]; Brody, Debra[2]; Hamad, Imad[2]; Rishi, Nitin[2]; Kanal, Emanuel[4]; Fung, John[2]

Author Information

Thomas E. Starzl Transplantation Institute, Department of Surgery, and Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213

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[2] Thomas E. Starzl Transplantation Institute, Department of Surgery.

[4] Department of Radiology.

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[3] Address correspondence to: Ashok Jain, MD, Thomas E. Starzl Transplantation Institute, 4C Falk Clinic, 3601 Fifth Avenue, Pittsburgh, PA 15213.

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Abstract

Background. Neurological complications after orthotopic liver transplantation (OLTX) have remained a major concern in a small proportion of patients. The etiology of these complications is often thought to be multifactorial: the influence of calcineurin inhibitors is occasionally thought to play an important role. When neurotoxicity occurs after OLTX under tacrolimus, it is usually a minor complication and responds readily to a reduction in the dosage of or a temporary withdrawal of tacrolimus. However, neurotoxic complications occasionally do not respond to this conventional process. Neoral is a microemulsion formulation of cyclosporine. It has more consistent pharmacokinetic parameters and improved bioavailability when compared with conventional cyclosporine. The aim of the present report was to evaluate the

role of Neoral in OLTX recipients with neurotoxic complication who failed to respond to a reduction in the dosage of tacrolimus.

Method. Between August 1995 and November 1997, 330 adults (age >18 years) received primary OLTX under tacrolimus-based immunosuppression (mean age 52.6±11.4 years). There were 190 men and 140 women. Twenty-three (7%) patients (mean age 53.2±11.8 years; 17 men, 6 women) were converted to Neoral (mean 35±41 days after OLTX). These patients were followed until June 1998 (mean follow-up 22.7±7.8 months).

Results. Four (17.4%) patients died during the follow-up period, and two patients underwent retransplantation. Neurological symptoms improved in all patients who survived. Adequate trough concentrations were achieved in all patients with p.o. Neoral. Nine (39%) patients experienced rejection episodes after conversion. Six (26.1%) patients were converted back to tacrolimus because of ongoing rejection (n=3), retransplantation (n=2), or persistent nausea and vomiting (n=1) without recurrence of the original neurological complication.

Conclusion. Neurological complications after OLTX disorders that occur under tacrolimus and that fail to respond to a reduction in the dosage can be treated safely by conversion to Neoral. However, the rate of rejection is up to 39%, and patients can often be converted back to tacrolimus without recurrence of the original neurological complication.

Abbreviations: CsA, cyclosporine, CT, computed tomography, HCV, hepatitis C virus, MRI, magnetic resonance imaging, OLTX, orthotopic liver transplantation.

Tacrolimus is a potent immunosuppressive agent, whose clinical benefit in solid organ transplantation is well recognized (1). However, after orthotopic liver transplantation (OLTX *), neurological complications have remained an important major concern in a small proportion of patients (2). This occurs both under cyclosporine (CsA) and

tacrolimus. Mild neurotoxicity usually improves by reducing or temporarily holding the dose of tacrolimus; however, some patients do not improve despite these measures. Because CsA and tacrolimus have different chemical structures, it was thought that OLTX recipients with significant or persistent neurotoxicity might benefit by conversion from tacrolimus to CsA. This would allow clearance of tacrolimus and its metabolites and at the same time provide adequate immunosuppression to prevent allograft rejection. Because the microemulsion formulation of CsA (Neoral) has pharmacological advantages over conventional CsA in terms of more reliable and consistent absorption, particularly its absorption in the absence of bile (4), Neoral was thought to be the preferred agent for conversion.

The aim of this report is to examine the need for and incidence of conversion from tacrolimus to Neoral for neurological complications in OLTX patients who failed to respond to tacrolimus dose reduction. It also describes the clinical course of the patients with regard to liver function, renal function, rate of rejection after conversion, the dosage and concentration of tacrolimus/Neoral, and changes in neurological status.

From August 1995 to November 1997, 330 adults (age >18 years) underwent primary OLTX at our center. The mean age was 52.6±11.4 years (range 18 to 73; median 53.0). There were 190 (57.6%) men and 140 (43.4%) women. All patients were commenced on tacrolimus 0.03 to 0.05 mg/kg/day intravenously as a continuous infusion and monitored with daily whole blood tacrolimus levels targeted at 15–20 ng/ml. When gastrointestinal function returned, tacrolimus was given orally with whole blood 12-hr trough concentrations of tacrolimus targeted at 12 to 15 ng/ml during the first postoperative month. All patients were followed up to June 1998, with a mean follow-up of 22.7±7.8 months (range 5.3 to 34.3; median 23.6). In all patients who experienced neurotoxicity after OLTX, the dose of tacrolimus was first reduced by 50% or held for 12–24 hr. If there was an improvement, then tacrolimus was restarted at a lower dose. In situations where there was no improvement, the patients were switched to Neoral and followed carefully. Before conversion, a computed tomography (CT) scan/magnetic resonance imaging (MRI) of the head, electroencephalogram, and spinal fluid were obtained in the majority of patients. Neoral was commenced orally or via nasogastric tube or feeding tube at a dose of 6 to 8 mg/kg/day in two divided doses. The clinical course of the patients and the


Table 1 Table 2

laboratory values before and after the conversion were recorded (Tables 1 and 2). All patients were followed by the investigator in the hospital and in the outpatient clinic.

Twenty-three (7.0%) of 330 patients were converted to Neoral in the postoperative period for neurological complications. There were 17 men and 6 women; the mean age was 53.2±11.8 years (range 20 to 72: median 54.2) at the time of OLTX. The mean time to conversion was 35.4±40.8 days (range 5 to 151; median 18) after OLTX. The reasons for conversion were mental status changes (n=7), grade II/III coma (n=4), confusion (n=3), expressive aphasia (n=3), cognitive changes with headache (n=2), Guillain-Barré syndrome (n=1), status epilepticus (n=1), mental status changes with depression (n=1), and peripheral neuropathy with grade II coma (n=1).

Eighteen (78.3%) of 23 patients were converted within the first 6 weeks after OLTX. However, five patients (cases 9, 18, 19, 20, and 21) were converted 139, 97, 70, 46, and 151 days after OLTX, respectively (Table 1). All five patients were on a lower dose of tacrolimus and are described below. Case 9 had very mild persistent cognitive dysfunction with abnormal MRI finding and was converted to Neoral on the 139th day after OLTX. Case 18 had a mild mental status change with inability to concentrate and persistent headache and was converted to Neoral as an outpatient on the 97th postoperative day. Case 19 had a prolonged confusional state of mind. CT of the head revealed a small subdural hematoma (Fig. 1 A) not sufficient for surgical intervention. He was converted to Neoral on the 70th post-OLTX day. He subsequently died from sepsis 4 months later. Case 20 received the right lobe of a split liver twice; he continued to have cognitive disorder and failed to understand his medications. CT of the head showed volume loss (Fig. 1B). He was converted to Neoral on the 46th postoperative day. Case 21 presented with parasthesia in both legs. Muscle and nerve biopsy specimens were consistent with Guillain-Barré syndrome. The patient demonstrated mild improvement in neurological symptoms, however, she experienced an episode of rejection, hence she was converted back to tacrolimus without further deterioration in neurological symptoms.

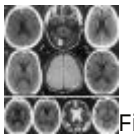
Figure 1

Twenty-one patients had either a CT scan or an MRI of the head. Six patients showed evidence of mild intracranial bleeding not sufficient to warrant surgical intervention (cases 2, 5, 11, 12, 13, and 19;Fig. 1A). Four patients showed volume loss (cases 6, 10, 15, and 20;Fig. 1B). One patient (case 9) had an MRI that showed multiple foci of T2 signal abnormality in the periventricular and subcortical white matter, suggestive of small vessel ischemic disease.

Cerebrospinal fluid was obtained in 10 patients and was uniformly normal. There was no sign of bacterial, fungal, or protozoal infection.

Electroencephalogram was performed in 16 patients; results showed dysrhythmia of grade I (n=3), II (n=3), or III (n=70). The remaining three patients had normal electroencephalograms (Table 1).

Six (26%) patients had alcohol-related liver disease, and 7 (30.4%) had hepatitis C virus (HCV) infection. A total of 21% and 29% of the patients underwent OLTX for alcohol-related liver and HCV-related liver failure, respectively. Thus neither HCV-related nor alcohol-related liver disease seemed to be a significant factor (Table 1). Twelve (52%) patients were in intensive care unit, 3 (13%) patients were hospitalized, whereas 8 (35%) patients came from home for the OLTX. This is the usual distribution at our center. Eighteen (78.3%) patients had a documented previous history of encephalopathy, whereas 5 (21.7%) patients did not.

After conversion, two patients (8.7%) underwent retransplantation, one for recurrent HCV (case 7, who subsequently died) and the other for uncontrolled rejection (case 23). Four (17.4%) patients died: two were secondary to intracranial hemorrhage (cases 7 and 14; 48 and 180 days after conversion, and 66 and 211 days after OLTX). In the third patient (case 4) life support was withdrawn after more than 4 months (5 months after OLTX) for persistent status epilepticus. In the fourth case (case 19), the patient died of sepsis 4 months after conversion

(6 months after OLTX) (Table 2).

Nine (39.1%) patients experienced episodes of rejection after conversion. In three patients, tacrolimus was reinstituted, in addition one underwent retransplantation; the other five patients had a complete response from additional corticosteroids, in addition were maintained on Neoral.

The mean tacrolimus dose was 0.15±0.14 mg/kg/day before conversion. The mean tacrolimus whole blood trough concentration (IMx, Abbott Laboratories, Abbott Park, IL) was 10.8±4.5 (median 10.6) ng/ml. At the most recent follow-up, the mean Neoral dose was 2.9 ± 1.3 (median 2.8) mg/kg/day. The mean trough whole blood CsA (TDx using Polyclonal antibody; by Abbott Laboratories, Abbott Park, IL) concentration was 251±145 ng/ml (median 266). All patients achieved therapeutic CsA levels without the use of intravenous CsA (Table 2).

Four patients were on dialysis before conversion. Two of them eventually died. The remaining two patients came off dialysis soon after conversion. The mean serum creatinine level was 1.4±1.8 mg/dl (median 1.1), and the mean blood urea nitrogen was 44.2±27.7 mg/dl (median 43) before conversion. The mean serum creatinine level was 1.7±0.7 (median 1.6), and the mean blood urea nitrogen was 30.4±13.2 (median 30.0) mg/dl at the most recent follow-up (Tables 1 and 2).

Liver function tests before and after conversions are shown in Tables 1 and 2. Eight (34.8%) patients were jaundiced, with the total bilirubin >2.0 mg/dl. The mean bilirubin was 3.7±7.2 mg/dl before conversion. All patients who survived have nearly normal liver function.

Six (26.1%) patients were converted back to tacrolimus. The indications for reconversion were ongoing rejection (n=3), retransplantation (n=2), and persistent nausea and vomiting (n=1). One of these six patients died of intracranial

hemorrhage (case 7). In the remaining five patients, the inciting neurological event did not reappear or deteriorate after reinstitution of tacrolimus (Table 2).

A number of neurological complications and psychiatric disorders after liver transplantation have been described with both CsA and tacrolimus. They include tremor, headache, insomnia, nightmares, vertigo, dysarthria, mood changes, photophobia, akinetic mutism (expressive aphasia), seizure disorders, psychosis, encephalopathy, focal deficit, movement disorders, delirium, coma, cerebral pontine myelinolysis, agitation, cortical blindness, deterioration in cognitive function, pseudo bulbar paralysis, hemiparesis, depression, akinesia, mental status changes, confusion, chorea, nystagmus, polyneuritis, stupor, psychomotor agitation, and focal neural deficit (5–12).

It is clear that some of the neurological toxicities related to tacrolimus or CsA are dose dependent and reversible with dosage reduction (3). The incidences of neurological complaints under CsA and tacrolimus are comparable (2), with rates of up to 33% under CsA and 34% under tacrolimus (7). However, the etiology is considered to be multifactorial and is related to a combination of events including liver dysfunction, renal impairment, electrolyte imbalance, metabolic disturbances, hypomagnesemia, hypocholesterolemia, surgical stress, organic brain changes (cerebral hemorrhage, abscess), and concomitant use of steroids (5). In a randomized trial of tacrolimus and CsA from Germany, and also in the American and European multicenter studies, a higher incidence of neurological disorders under tacrolimus was observed. These incidences were lower when lower dosages of tacrolimus were used (1–3).

In our center, when neurotoxicity occurs, it is customary to reduce the dosage of tacrolimus significantly or even hold it for 12–24 hr; if there is no improvement, the patients are converted to Neoral. Patients with seizure disorders are usually managed with antiepileptics (phenytoin, phenobarbital, diazepam) and adjustment of the tacrolimus dose. These patients are usually not converted to Neoral unless the seizures are not controlled (as in case 4 in this study). Patients

with expressive aphasia usually are converted to Neoral as soon as the diagnosis is made. Six patients had small intracranial hemorrhages, which could have contributed to neurotoxicity; however, the bleeds were too small to warrant surgical intervention. These patients were empirically switched to Neoral in the hope that the associated small impact of tacrolimus or its metabolites would be eliminated, and the introduction of Neoral with a different chemical structure might be helpful. In any event, it is clear that tacrolimus was not the only cause of neurotoxicity. Patients with a prior history of encephalopathy, a complicated postoperative course, sepsis, and severe hepatic dysfunction have been thought to be more likely to develop neurotoxicity irrespective of whether they receive tacrolimus or CsA (2). In the present study, eight patients had significant hepatic dysfunction, and four patients were on dialysis. We hypothesize that various analgesics, sedatives, and/or anesthetic agents and their respective metabolites may interact with calcineurin inhibitors and their metabolites and may cause some of the neurological disorders, often in the presence of hepatic and renal dysfunction, where this metabolite could take an unusually long time to be eliminated after discontinuation of tacrolimus. Conversion from one calcineurin inhibitor to another with a different chemical structure may be a useful alternative in the management of neurotoxicity after OLTX.

In summary, neurological complications in OLTX patients receiving tacrolimus, which do not improve after a reduction in dosage, can be managed safely with Neoral. However, 39% of the patients may experience rejection; after conversion to Neoral, they can be reconverted to tacrolimus without recurrence of the original neurological complication.

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REFERENCES

1. Jain A, Fung J. Cyclosporine and tacrolimus in clinical transplantation: comparative review. Clin Immunother 1996; 5 (5):351. [Context Link]

2. Mueller AR, Platz KP, Bechstein WO, et al. Neurotoxicity after orthotopic liver transplantation. Transplantation 1994; 58 (2):155. Ovid Full Text Find Full-Text [Context Link]

3. Eidelman BH, Abu-Elmagd K, Wilson J, et al. Neurological complications of FK506. Transplant Proc 1991; 23 (6):3175. Find Full-Text [Context Link]

4. Oldhafer K, Haller GW, Kattner A, et al. Absorption of cyclosporine Neoral early after liver transplantation: influence of bile on oral absorption. Transplant Proc 1996; 28 (4):2237. Find Full-Text [Context Link]

5. Thompson CB, Sullivan KM, June CH, Thomas ED. Association between cyclosporin neurotoxicity and hypomagnesaemia. Lancet 1984; 2:1116. Find Full-Text [Context Link]

6. Adams DH, Gunson B, Honigsberger L, et al. Neurological complications following liver transplantation. Lancet 1987; 1:949. Find Full-Text [Context Link]

7. Burkhalter EL, Starzl TE, Van Thiel DH. Severe neurological complications following orthotopic liver transplantation in patients receiving FK 506 and prednisone. J Hepatol 1994; 21:572. Find Full-Text [Context Link]

8. Freise CE, Rowley H, Lake J, Hebert M, Ascher NL, Roberts JP. Similar clinical presentation of neurotoxicity following FK 506 and cyclosporine in a liver transplant recipient. Transplant Proc 1991; 23 (6):3173. Find Full-Text [Context Link]

9. DiMartini A, Pajer K, Trzepac P, Fung J, Starzl T, Tringali R. Psychiatric morbidity in liver transplant patients. Transplant Proc 1991; 23 (6):3179. Find Full-Text [Context Link]

10. Christie W. Neurological disorders in liver and kidney transplant recipients. Transplant Proc 1994; 26 (6):3175. Find Full-Text [Context Link]

11. Frank B, Perdizet, GA, White JW, Lemann W, Woodle ES. Neurotoxicity of FK in liver transplant recipients. Transplant Proc 1993; 25 (2):1887. Find Full-Text [Context Link]

12. Durant S, Chipping PM, Palmer S, Gordon-Smith EC. Cyclosporin A, methyl prednisone, and convulsions. Lancet 1982; 2:829. Find Full-Text [Context Link]

TABLE 1. Before conversion

Case	Age	Sex	Diagnosis	Days after OLTX	Reason for switch	CT head	EEG*	Tacro dose (mg/kg/day)	Tacro level (ng/ml)	BUN (mg/dl)	Creatinine (mg/dl)	T. Bili. (mg/ml)	AST (μ/ml)	ALT (μ/ml)	GGTP (μ/ml)
1	63	F	PNC-C	28	Mental status changes	NA	Dysrhythmia, gr1	0.10	5.0	28.0	1.1	0.6	30	23	166
2	48	M	A1A	18	Stage III coma	Small subdural hematoma	Dysrhythmia, gr2	0.08	20.9	D	D	1.5	38	51	172
3	66	M	HCV	11	Mental status changes	NA	Dysrhythmia, gr3/myoclonic seizure	0.21	11.1	50.0	1.6	2.8	47	100	379
4	20	M	AFF	22	Status epilepticus	Normal	Dysrhythmia, gr3/spike and wave pattern	0.70	11.6	16.0	0.5	0.8	54	50	302
5	55	M	PBC	10	Confusion	NA	NA	0.18	10.6	D	D	4.0	62	143	297
6	50	M	PNC-E	7	Mental status changes	Volume loss	Dysrhythmia, gr2; generalized seizure	0.04	21.3	46.0	1.4	0.8	18	40	387
7	42	M	HCV + HBV	31	Grade II coma	Normal	Dysrhythmia, gr3	0.14	6.3	D	D	35.1	296	372	320
8	43	F	A1A	39	Depression, mental changes	Volume loss	Normal	0.11	15.8	28.0	1.2	0.7	15	25	45
9	53	M	HCV	139	Severe headache and mild cognitive changes	Decrease attenuation in frontal lobe	NA	0.03	11.1	45.0	2.6	0.6	7	17	30
10	45	M	PNC-E	8	Mental status changes	Volume loss	Dysrhythmia, gr1	0.18	7.3	59.0	1.0	3.4	48	49	232
11	54	M	PNC-E	14	Mental status changes	Subarachnoid hemorrhage	NA	0.11	9.6	22.0	1.4	0.7	36	73	323
12	67	F	PNC-E	22	Mental status changes	Bifrontal subdural collection	Dysrhythmia, g2	0.18	5.0	43.0	1.1	0.6	18	91	78
13	48	M	HBV	17	Expressive aphasia	Small subdural hematoma	Normal	0.33	8.8	14.0	1.0	1.0	150	358	714
14	49	F	NASH	18	Grade II coma	Normal	Dysrhythmia, g2–3	0.12	9.4	66.0	1.1	4.6	51	106	49
15	61	M	HCV	16	Expressive aphasia	Volume loss	Dysrhythmia, gr1	0.26	11.4	106.0	1.5	1.9	20	38	355
16	60	M	A1A	5	Grade II coma	Normal	NA	0.10	17.8	63.0	2.2	4.6	178	257	126
17	50	M	HCV	6	Expressive aphasia	Normal	Dysrhythmia, gr3	0.10	11.1	58.0	1.6	0.7	152	87	1122
18	61	F	PENC-E	97	Severe headache and mild cognitive changes	NA	NA	0.16	11.5	21.0	0.8	0.7	27	38	133
19	60	M	PNC-C	70	Confusion	Subdural hematoma	Dysrhythmia, gr3	0.03	6.0	D	D	0.9	55	140	69
20	34	M	PENC-E	46	Mental status changes	Volume loss	Normal	0.15	6.2	14.0	0.9	1.6	27	14	40
21	61	F	PNC-C	151	Guillain-Barré	NA	NA	0.10	12.0	36.0	0.7	0.8	88	18	224
22	72	M	HCV/HBV	10	Mental status changes	Normal	NA	0.07	10.6	18.0	0.8	4.7	55	119	66
23	64	M	HCV	29	Grade II coma + peripheral neuropathy	Normal	Dysrhythmia, gr3	0.00	7.6	106.0	4.8	12.9	330	161	359
Mean	53.2			35.4				0.15	10.8	44.2	1.4	3.7	78	103	260
SD	11.8			40.8				0.14	4.5	27.7	1.0	7.2	85	99	243
Median	54.2			18.0				0.11	10.6	43.0	1.1	1.3	50	80	228

* Abbreviations used in table: A1A, alpha1 antitrypsin deficiency; AFF, acute fulminant failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C, cryptogenic; D, dialysis; E, ethanol; EEG, electroencephalogram; GGTP, gamma glutamyl transferase; gr, grade; HBV, hepatitis B virus; NA, not available; NASH, nonalcoholic steato hepatitis; PBC, primary biliary cirrhosis; PNC, postnecrotic cirrhosis; Tacro, tacrolimus; T. Bili, total bilirubin.

Table 1 . Before conversiona Abbreviations used in table : A1A, alpha1 antitrypsin deficiency; AFF, acute fulminant failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C, cryptogenic; D, dialysis; E, ethanol; EEG, electroencephalogram; GGTP, gamma glutamyl transferase; gr, grade; HBV, hepatitis B virus; NA, not available; NASH, nonalcoholic steato hepatitis; PBC, primary biliary cirrhosis; PNC, postnecrotic cirrhosis; Tacro, tacrolimus; T. Bili, total bilirubin.

TABLE 2. Post conversion last follow-up

Case	Months from switch	Neoral dose (mg/kg/day)	CsA level (ng/ml)	BUN (mg/dl)	Creatinine (mg/dl)	T. Bili. (mg/ml)	AST (μ/ml)	ALT (μ/ml)	GGTP (μ/ml)	Outcome
1	34.3	2.6	279	34.0	1.6	0.6	26	25	31	Improved-continue Neoral
2	32.2	NA	NA	11.0	1.1	0.7	47	64	156	65 Days, rejection, switch back tacro
3	28.4	1.8	215	22.0	1.5	0.8	13	27	31	Improved-continue Neoral
4	NA[a]	NA	NA	NA	NA	NA	NA	NA	NA	126 days, later withdrawal life support-died
5	30.4	NA	NA	27.0	2.0	0.8	34	56	145	14 days later rejection, switch back tacro
6	25.6	0.3	<50	41.0	3.5	0.4	40	37	195	Improved-continue Neoral
7	NA	NA	NA	NA	NA	NA	NA	NA	NA	Recurrent HCV, retx, switch to tacro, died from intracranial bleed
8	27.1	2.7	266	19.0	1.2	0.9	24	31	70	Improved-continue Neoral
9	29.0	2.0	16	25.0	1.7	1.3	69	34	214	Improved-continue Neoral
10	24.0	3.1	467	41.0	1.9	0.8	21	22	101	Improved-continue Neoral
11	23.6	1.9	242	41.0	3.0	0.4	26	48	127	Improved-continue Neoral
12	21.6	4.4	274	22.0	1.1	0.8	103	142	372	Improved-continue Neoral
13	21.6	5.2	270	36.0	1.9	1.3	29	53	28	Improved-continue Neoral
14	NA	NA	NA	NA	NA	NA	NA	NA	NA	Died 48 days later, intracranial bleed
15	20.4	1.5	68	30.0	1.8	1.3	37	50	94	Improved-continue Neoral
16	20.1	2.9	455	32.0	1.6	0.9	31	22	41	Improved-continue Neoral
17	26.8	NA	NA	34.0	1.2	0.9	76	51	446	Improved-nausea and vomiting, switch back to tacro
18	23.4	3.6	100	12.0	0.9	0.6	28	26	155	Improved-continue Neoral
19	NA	NA	NA	NA	NA	NA	NA	NA	NA	4 Months later, died of sepsis
20	11.9	4.4	452	13.0	1.1	1.6	31	24	30	Improved-continue Neoral
21	17.1	NA	NA	24.0	0.9	0.2	19	9	88	Improved, 71 days later rejection, switch back to tacro
22	5.3	3.9	156	60.0	1.5	0.8	36	16	58	Improved-continue Neoral
23	7.5	NA	NA	53.0	1.9	0.7	63	42	207	26 Days later rejection, retx, switch back to tacro
Mean	22.7	2.9	251	30.4	1.7	0.8	39.6	41.0	136.3	
SD	7.8	1.3	145	13.2	0.7	0.3	22.8	28.7	114.8	
Median	23.6	2.8	266	30.0	1.6	0.8	31.0	34.0	101.0	

[a] Abbreviations used in table: NA, not applicable; retx, retransplant; for other abbreviations see footnote to Table 1.

Table 2 . Post conversion last follow-upa Abbreviations used in table : NA, not applicable; retx, retransplant; for other abbreviations see footnote to Table 1.

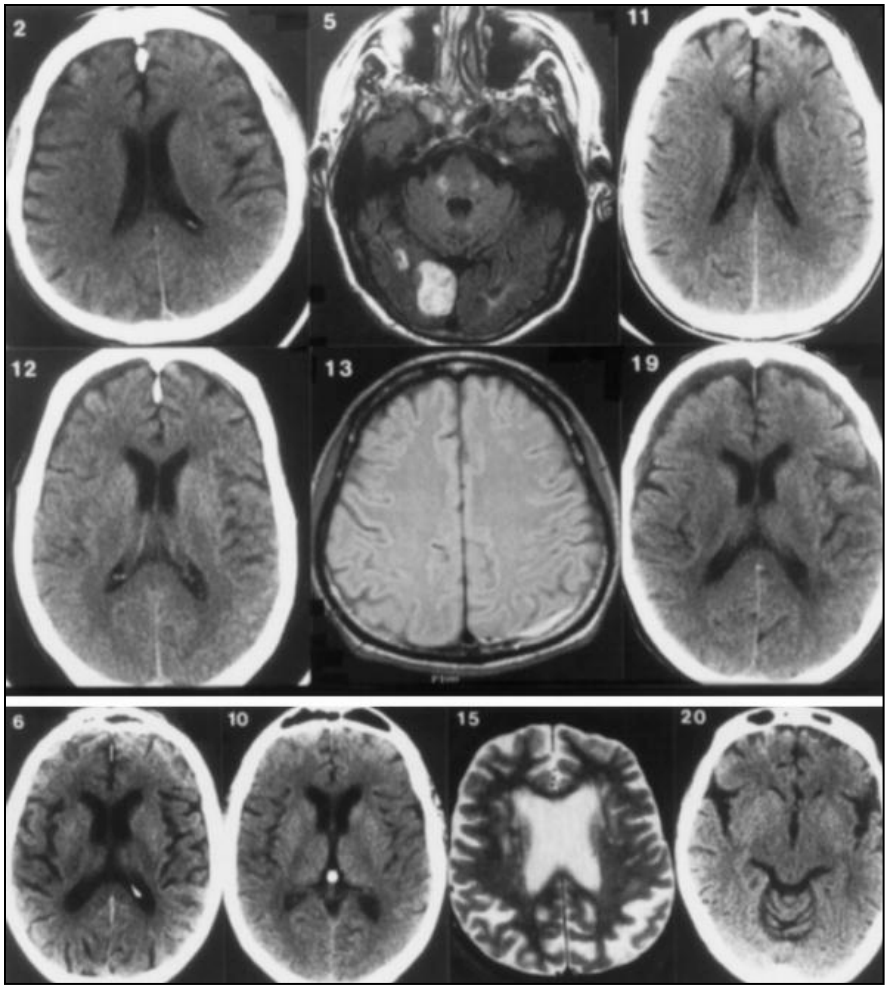

Figure 1 . CT of the head. (A) Cases 2, 5, 11, 12, 13, and 19: CT shows mild intracranial bleeding not sufficient for surgical intervention. (B) Cases 6, 10, 15, and 20, CT shows volume loss of cerebral hemisphere.