Case Report

NEPHRON

Nephron 2001;87:361–364

Accepted: May 18, 2000

Cyclosporine-Associated Thrombotic Microangiopathy during Daclizumab Induction: A Suggested Therapeutic Approach

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Key Words

Kidney transplantation · Thrombotic microangiopathy · Cyclosporine · Daclizumab · Plasma infusions · Plasmapheresis · FK-506 · D-dimer · Fibrinogen-degradation products · Panel-reactive antibodies

Abstract

A woman on daclizumab developed thrombotic microangiopathy secondary to cyclosporine after a living-unrelated kidney transplant. Despite cyclosporine discontinuation, hemolysis persisted. The second dose of daclizumab was postponed 24 h, and after a maximum of two sessions of plasmapheresis (to avoid further modifications in daclizumab schedule) with plasma exchange, daclizumab was administered. Plasma infusions were prescribed until D-dimer and fibrinogen-degradation products normalized; thereafter, FK-506 was started without recurrence of the hemolytic picture and renal function restored. This observation suggests that in patients on daclizumab who develop thrombotic microangiopathy secondary to immunosuppressants, if discontinuation of the offending drug is unsuccessful, plasmapheresis with plasma exchange can be performed when the lowest levels of daclizumab exist, followed by daclizumab infusion. Plasma prescription must be continued thereafter until D-dimer and figrinogen-degradation products normalize. However, if hemolysis persists when daclizumab levels are high, plasma infusions are useful and plasmapheresis avoided. FK-506 administration did not result in recurrence of hemolysis during daclizumab induction.

Cyclosporine (CsA)-associated thrombotic microangiopathy (TMA) has an incidence of approximately 3–14% in renal transplantation [1, 2], and is a potential cause of allograft loss. Renal dysfunction, reflected by an increase in serum creatinine (Scr), is the only alteration always found, as the clinical features of intravascular hemolysis are not always present. The gold standard of TMA is a kidney biopsy [3]. The usual therapeutic approach consists initially in either decreasing the administered CsA dose or discontinuation of the drug. If renal function does not improve, plasmapheresis (Pph) with plasma infusions or even plasma alone are valid options [4]. However, when monoclonal antibodies such as daclizumab (Dacl) are being used as induction therapy every 14 days for five successive doses, were Pph performed when therapeutic levels of Dacl exist, these effective and

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0028–2766/01/0874–0361$17.50/0

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Table 1. Summarized laboratory data

Results:	Day 0	Day 3	Day 7	Day 8	Day 9	Day 10	Day 14	Day 15	Day 19	Day 25	Day 28	Day 33	Day 38	Day 44	Day 60	Day 90	Day 240
Therapy:	Dacl 1st dose	CsA init.			CsA disc.		Pph, P	Pph, P Dacl 2nd	P	P	FK-506 init.	FK-506	FK-506	FK-506	FK-506	FK-506	FK-506
Hct, %	30	27	29	28	28	27	25	24	24	27	28	30	32	34	34	35	37
WBC, mm^3	7,800	8,800	9,800	8,100	9,000	11,200	6,200	6,500	8,700	3,600	3,900	4,500	6,300	6,400	6,100	6,400	5,100
Platelets mm^3	288,000				72,000	65,000	65,000	45,000	76,000	99,000	11,000	134,000	150,000	170,000	200,000	170,000	190,000
Schistocytes					++++	++++	++++	+++	++	–	–	–	–	–	–	–	–
LDH, U/l					966	842	534	221	299	312	319	302	275	250	310	290	250
Urea, mg/dl	104	57	46	88	123	178	199	199	155	98	80	75	56	46	42	66	36
Creatinine mg/dl	7.32	1.9	1.3	2.9	5	5.3	3	3.3	1.9	1.5	1.4	1.3	1.1	1.1	1.0	0.9	0.8
Fibrinogen mg/dl					44	48	99	179	222	273	298	290	248	222	280	210	240
D-dimer, μg/ml					>1	>1	>1	>1	>0.5	>0.5	–	–	–	–	–	–	–
FDP, μg/ml					24	25	20	15	15	10	–	–	–	–	–	–	–

Dacl = Daclizumab; CsA = cyclosporine; Pph = plasmapheresis; P = plasma; init. = initiated; disc. = discontinued; FDP = fibrinogen-degradation products; + = positive; – = negative. Normal values: LDH 200–460 U/l; urea 10–50 mg/dl; creatinine 0.50–1.2 mg/dl; fibrinogen 200–400 mg/dl; D-dimers <0.5 μg/ml; fibrinogen-degradation products >10 μg/ml.

expensive drugs would be cleared from the serum with the procedure, increasing the risk of rejection. To avoid such circumstances, we present our experience with a patient on Dacl who suffered from CsA-induced TMA 9 days posttransplant and was managed with discontinuation of the drug until the second dose of Dacl was scheduled, when two sessions of Pph with plasma exchange were performed for 2 days followed by the administration of Dacl and daily infusions of plasma. Thereafter, when D-dimer and fibrinogen-degradation products were within normal limits, plasma infusions were stopped and FK-506 was initiated, with good results at 8 months' posttransplantation.

Case Report

A 47-year-old Hispanic multiparous woman received a living-unrelated kidney from her husband due to end-stage renal disease secondary to polycystic kidneys. There was a two-HLA mismatch between donor and recipient, the former being cytomegalovirus negative and the latter positive. The patient also had elevated panel-reactive antibodies (PRA) (80%). The day of the transplant the patient received Dacl 1 mg/kg intravenously and immunosuppression consisted on intravenous methylprednisolone 300 mg and mycophenolate mofetil 3 g/day, plus ganciclovir for cytomegalovirus prophylaxis. The patient did well for the next days; by day 3 posttransplant, Scr was 1.9 mg/dl (table 1) and CsA microemulsion was started at 4 mg/kg/day. Whole blood trough levels of CsA were between 234 and 289 ng/ml. On day 8 posttransplant, the patient was asymptomatic but the urinary output began to decline and Scr rose to 2.9 mg/dl; schistocytes were found on a peripheral smear. Lactic dehydrogenase (LDH) was 848 U/l and the hematocrit and platelet count decreased (table 1). On day 9, a kidney biopsy was performed which was consistent with TMA with no signs of rejection; CsA was discontinued and the Scr gradually and slowly began to decline (table 1). On day 14, due to persistent low platelet counts, low fibrinogen, high D-dimer and fibrinogen-degradation products blood levels and a Scr of 3 mg/dl, Dacl administration (scheduled on day 14) was postponed 24 h and Pph with fresh-frozen plasma exchange was started. On day 15, the second course of Pph was performed and Dacl was given thereafter. On the subsequent days, 3 units of plasma were given daily, and Pph was stopped to avoid the clearance of Dacl with the procedure. On day 27, posttransplant D-dimer and fibrinogen-degradation products' blood levels were negative and plasma infusions discontinued. By day 28, Scr was 1.52 mg/dl, platelet count was 101×10^9/liter and the patient was discharged. After 8 months of follow-up, Scr was 1.1 mg/dl and no signs of hemolysis appeared.

Discussion

CsA-associated TMA is a well-documented and severe cause of renal failure in organ transplantation [1, 2], and appears to be more frequent with the microemulsion form of CsA [2]. In organ transplantation, glomerular capillary and arteriolar thrombi can be seen not only in association with CsA, but also in biopsy samples showing ischemic injury or acute rejection with intimal arteritis (reported long before CsA was available) taken from patients with sepsis, hemolytic uremic syndrome, systemic lupus erythematosus, and malignant hypertension, or receiving FK-506. Thus, a diagnosis of CsA-induced TMA can be made only after these causes have been ruled out [5, 6]. The diagnosis of TMA in our patient is supported by both

renal biopsy findings and clinical follow-up. Although TMA in transplantation is thought to be multifactorial [7], we believe CsA was the main cause of hemolysis, as a partial drop in Scr followed immediate CsA discontinuation. The reason why renal function did not return to baseline after CsA withdrawal may be due to additional extensive endothelial damage caused by other factors, as the role PRA may play. Zent et al. [7] found an association between CsA-induced TMA and high PRA levels in kidney transplants without rejection; in that study, although 11% of patients had undergone previous transplantation, 89% had PRA; after CsA withdrawal TMA responded in 61% of patients to antirejection therapy (in 11% of patients Pph was added) and reintroduction of CsA, concluding that endothelial cell damage in the post-transplant period may be multifactorial. Being multiparous could have rendered our patient highly sensitized although, in contrast to cadaveric transplants, many husband-to-wife renal transplants are highly successful despite the possibility of prior immunization through pregnancy [8], and in this case report there was only a two-HLA mismatch.

As initial management, a reduction in the dose or direct discontinuation of CsA correlates with an improvement in renal function in most patients, but the risk of rejection increases [4]. Plasmapheresis, plasma exchange or anticoagulation are alternate therapeutic options [4, 9] albeit, to our knowledge, no controlled treatment trials for transplant patients with TMA have been performed to assess the benefits of such treatments. With respect to CsA as a cause of TMA, CsA exerts direct toxic effects on the endothelium, resulting in LDH release and increases in generation of thromboxane A_2 and prostacyclin [2]. Also important is the vasoconstrictor effect of CsA increasing endothelin and thromboxane levels and decreasing prostacyclin synthesis [2, 7]. Furthermore, CsA increases adenosine diphosphate-induced platelet aggregation, thromboplastin and von Willebrand complexes generation and factor VII activity [4], all participants in the pathogenesis of TMA. In addition, other prothrombotic substances as platelet-activating factor, plasminogen activator inhibitor-1 and von Willebrand factor are increased in TMA [2, 10]. Thus, the rationale for Pph or plasma infusions when the cause of TMA is CsA is that Pph removes von Willebrand complexes and other prothrombotic agents; plasma supplies antithrombotic substances. Thrombocytopenia is due to shortened platelet survival caused by increased turnover, and a platelet-activated state may persist for weeks after the platelet count normalized [10]. Finally, schistocytes are caused by free radicals released from neutrophils, which mediate lipid peroxidation of red blood cell membranes and turn membranes to become rigid structures, undergoing increased shear stress as they pass through altered microvessels [10].

Our patient was started on Dacl, a humanized IgG1 monoclonal antibody that binds specifically to the α-subunit (CD-25 molecule) of the human high-affinity interleukin-2 receptor, expressed on the surface of activated lymphocytes. Dacl lowers the risk of acute rejection in kidney transplantation, reduces the need for secondary immunosuppressants and does not increase the risk of opportunistic infections or malignancy [11]. As shown in table 1, due to TMA and when Dacl trough blood levels were reached (day 14), Pph was started with plasma exchange for 2 consecutive days. We decided not to continue with Pph so as not to interfere with Dacl schedule; three daily units of plasma were effective. We were unable to measure Dacl levels and the variation of interleukin-2 receptor saturation on circulating lymphocytes before and after plasmapheresis or plasma infusions, but the clinical outcome suggests these therapeutic tools to be valid options.

Complications due to plasma infusions include volume overload, viral infections and renal injury [10]. Finally, switching from CsA to FK-506 or vice versa may be associated with initial resolution of TMA, but this condition may later recur [2, 9]. The conversion strategy from CsA to FK-506 can result in graft failure in approximately 14% to as high as 57% [2]. As FK-506-associated TMA is also a well-described entity [9], we advocate to follow D-dimers and fibrinogen-degradation products' blood levels (known to be elevated in TMA [12] and the best predictors that we found to correlate with the resolution of the hemolysis) to decide when to start FK-506, as recurrence might occur. It should be noted that as in our patient, despite normalization of LDH, fibrinogen and Scr levels, a persistent underlying hemolytic disorder can persist (table 1). Controlled prospective clinical trials in renal transplantation on TMA are needed to assess the efficacy of switching from CsA to FK-506 and vice versa.

To our knowledge, no reports on CsA-associated TMA during Dacl treatment have been published before and experience with therapeutic options for CsA-associated TMA is anecdotal. We believe that whenever TMA is suspected, a kidney biopsy must be performed because TMA can coexist with hyperacute or acute rejection [2]. CsA should be discontinued immediately and if Scr does not fall to baseline, Pph plus plasma infusions must be considered: If this decision has to be made when trough levels of Dacl exist, Pph with plasma exchange can be performed

for up to two sessions (to avoid a prolonged discontinuation of the monoclonal antibody increasing the risk of rejection), followed by daily infusions of plasma. At any other time, plasma alone can be given.

In summary, the present report shows that in the context of renal transplant patients on Dacl induction therapy who develop TMA after CsA prescription, if Scr does not return to baseline following CsA discontinuation, Pph plus plasma exchange is a valid option when trough levels of Dacl exist. If not, plasma infusions alone can be effective. If switching from CsA to FK-506 is considered, we advocate to start FK-506 when D-dimer and fibrinogen-degradation products are negative, to lower the risk of eventual recurrence of TMA. Finally, in recipients with elevated PRA who receive CsA, TMA may be a more frequent complication.

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