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FK506 “RESCUE” FOR RESISTANT REJECTION OF RENAL ALLOGRAFTS UNDER PRIMARY CYCLOSPORINE IMMUNOSUPPRESSION¹

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Abstract

Seventy-seven patients with ongoing acute rejection on initial CsA therapy were converted to FK506 to attempt graft salvage. Fifty-nine patients had undergone primary transplantation and 18 had been retransplanted; there were 52 cadaveric and 25 living-donor transplants. The indications for conversion to FK506 were ongoing, biopsy-confirmed rejection in all patients, including vascular rejection in 20. The median interval to rescue was 2 months (range 2 weeks to 36 months) after transplantation. Sixty-one of the 77 patients (79%) had already received one or more courses of an antilymphocyte preparation (OKT3: n=33; ALG or ATG: n=1; OKT3+ALG/ATG: n=27). Of the 77 patients, 57 (74%) have been successfully rescued and still have functioning grafts with a mean follow-up of 14 months, with a mean serum creatinine of 2.35±0.97 mg/dl. Eighteen patients were already dialysis-dependent at the time of conversion to FK506; of these, 9 (50%) were successfully salvaged and have a mean serum creatinine of 2.3 mg/dl. Of the 61 patients previously treated with antilymphocyte preparations, 48 (79%) were rescued. In those salvaged, prednisone doses have been lowered from 22.2±7.2 mg/day preconversion to 7.5±5.6 mg/day postconversion, and 12 patients are on FK506 monotherapy. In nondiabetics, mean serum glucose was 101.4±20.5 mg/dl preconversion and 93.2±22 postconversion ($P=0.07$), uric acid 7.3±2.3 and 7.1±1.5 mg/dl ($P=0.53$), and triglycerides 199.2±101.6 and 167.2±106.4 mg/dl ($P=0.06$). Cholesterol levels were significantly lower following FK conversion (207.7±46.5 mg/dl pre. vs. 188.3±39.7 post., $P=0.007$). FK506 is capable of salvaging renal allografts with ongoing acute rejection on CsA therapy, even when antilymphocyte preparations have been ineffective.

Resistant allograft rejection under cyclosporine-based immunosuppression remains a considerable problem despite novel strategies designed to optimize the use of CsA, including sequential therapy with antilymphocyte preparations (1–5). Furthermore, the safety of steroid withdrawal under CsA immunosuppression and CsA monotherapy is unclear (6). The current

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modalities available to treat steroid-resistant rejection episodes under CsA-based immunosuppression are limited and may require retreatment with antilymphocyte regimens that have also been used for prophylaxis. These limitations often place the practitioner at a significant disadvantage when trying to achieve graft retention while sparing the recipient the morbidity associated with the intensive immunosuppression that accompanies most of these agents. Clearly, the development of novel antirejection agents that can be used to “rescue” grafts failing other standard protocols is needed. FK506 is an experimental immunosuppressive agent that has been used with encouraging results as primary therapy in renal transplantation (7). Steroid tapering and FK506 monotherapy can be achieved in a majority of patients with apparently no increased risk of rejection (8), which is usually not possible with CsA because of increased risk of rejection and nephrotoxicity (1). We have recently begun to evaluate FK506 as a salvage agent for renal allografts failing conventional immunosuppression under CsA. In a preliminary group of patients we previously reported that FK506 cannot be used to salvage allografts with chronic rejection or CsA toxicity, but may hold promise for grafts with ongoing acute rejection (9). We now report our expanded experience with FK506 conversion of patients deemed to be losing their grafts from ongoing acute rejection while on CsA therapy.

MATERIALS AND METHODS

Patients

Between July 14, 1989 and February 16, 1993, seventy-seven patients (44 male, 33 female) with a mean age of 33.3 ± 12.4 years (range 2–59 years) were switched to FK506 immunosuppression after failing CsA-based immunosuppression. Fifty-nine patients (77%) were primary transplant recipients and 18 (23%) had been retransplanted (12 second, 4 third, and 2 fourth transplants). Fifty-two patients (68%) were recipients of cadaveric grafts and 25 (32%) were from living donors (21 related, 4 unrelated). Four patients had received combined kidney-pancreas transplants. 1 patient was given a kidney and pancreatic islets, and 3 patients were transplanted with pediatric “en bloc” kidneys from CAD donors under 24 months of age (10). The causes of end-stage renal disease included glomerulonephritis in 20 patients, insulin-dependent mellitus in 14, renal hypoplasia/dysplasia in 5, adult polycystic kidney disease in 4, hypertension in 4, systemic lupus erythematosus in 4, focal segmental glomerulosclerosis in 2, posterior urethral valves in 2, and Alport’s syndrome, Wegener’s granulomatosis, calculous disease, medullary cystic disease, reflux nephropathy, tuberous sclerosis, connective tissue disorder, and Lawrence Moon Biddell syndrome in 1 patient each. In 14 patients, the cause of ESRD was unknown.

All 77 patients converted to FK506 had uncontrolled rejection on primary CsA-based immunosuppressive therapy. The majority of the patients in this series (64 of 77, 78%) were referred to our institution from other centers where they were deemed to be losing their grafts; 13 patients (22%) were entered from our own institution. Whenever possible, careful consideration was given to ensure that all patients had been maintained on maximized but safe and tolerable CsA dosing. Maintenance immunosuppression had consisted of CsA and prednisone in all patients, either with ($n=55$, 71%) or without ($n=22$, 29%) azathioprine. Previous antirejection therapy had been administered to all 77 patients in the form of bolus high-dose corticosteroids. A total of 61 patients (79%) had also received at least 1 course of a monoclonal (OKT3) and/or polyclonal (ALG, ATG, or ATGAM) antilymphocyte preparation. Nineteen patients (25%) had received 2 or more courses of OKT3 prior to conversion and 27 patients (35%) received OKT3 and a polyclonal antilymphocyte preparation prior to FK506. Of the 61 patients, only 5 had received antilymphocyte prophylaxis alone without a subsequent course of either OKT3 or a polyclonal preparation to treat rejection prior to FK506.

Protocol for FK506 conversion

Doppler ultrasound and radionuclide flow study of the allograft were performed in all cases to rule out a technical cause for allograft dysfunction prior to FK506 conversion. In addition to reviewing pathologic specimens sent from the referring center, repeat core biopsies of the allograft were performed in all patients at our institution as part of the evaluation for FK506 conversion. Acute cellular rejection was present upon referral in all 77 cases, including 20 patients (26%) whose biopsies revealed a vascular component of rejection (lymphocytic infiltration in arterial walls, intraglomerular hemorrhage, and/or infarction). All patients underwent a simple switch ("clean conversion") from CsA to FK506 because of previous evidence of enhanced nephrotoxicity with combined FK506 and CsA therapy in liver allograft recipients (11). FK506 was given at a standard daily oral dose of 0.3 mg/kg/day in divided doses every 12 hr starting 12 hr after the last CsA dose. Parental doses of FK506 of 0.025 to 0.1 mg/kg/day overlapping with the first 1 to 4 days of oral therapy were also given to 16 patients. Dosage adjustments were based upon monitoring of trough serum FK506 levels by ELISA (12) to achieve a 12-hr trough level of 1.0 to 2.0 ng/ml, and also by adjustment according to clinical and biochemical parameters. Data were analyzed for statistical significance by paired two-tailed Student's *t* test or chi-square analysis when appropriate.

RESULTS

Seventy-seven patients failing primary CsA-based immunosuppression with ongoing rejection were converted to FK506 at an average of 4.3 ± 6.3 months (range 0.5 to 36 months) following transplantation. The criteria for establishing successful graft salvage with FK506 included a return to or improvement in baseline serum creatinine (SCR),* and/or improvement on follow-up renal allograft biopsy, and/or freedom from dialysis if the patient was dialysis-dependent at the time of conversion to FK506. With a mean follow-up of 13.9 ± 9.1 months (range 2–34 months), 57 of 77 patients (74%) have achieved graft salvage according to the aforementioned criteria. All 77 patients converted to FK506 had evidence of ongoing cellular rejection on preconversion allograft biopsy. Of these, 20 patients (26%) also had evidence of a vascular component of rejection, and 10 patients (13%) converted to FK506 had never achieved initial graft function. The outcome of FK506 conversion in each of these groups is shown in Table 1. The best success was achieved in patients with elements of acute cellular rejection only on preconversion biopsy, with 40 of 47 (85%) achieving graft salvage. Ten patients with grafts that had never functioned and who remained on dialysis from the time of transplantation were entered into this trial. An additional 8 patients with primary graft function became dialysis-dependent as a result of severe ongoing rejection during initial CsA therapy before conversion to FK506. Overall, 18 of 77 patients (23%) were dialysis-dependent at the time of conversion to FK506. Nine of these patients (50%) currently have functioning grafts with a mean SCR of 2.3 ± 1.7 mg/dl at a mean follow-up of 18.4 ± 11.2 months (median 18 months) postconversion.

Successful rescue with FK506 was obtained in 37 of 52 (73%) CAD and in 20 of 25 (80%) LD recipients ($P=NS$). Sixty-four of the 77 patients were referred to our institution from outside centers for FK506 conversion; of these, 50 (78%) were successfully rescued compared with 7 of 13 (54%) entered from our own institution. Of 4 patients with combined kidney-pancreas transplants, 3 (75%) were rescued. Three patients were recipients of pediatric en bloc kidneys from CAD donors under 24 months of age; of these, 2 (67%) were successfully salvaged. Equivalent success was obtained in the 59 primary transplantations (44 salvaged, 74%) and the 18 retransplantations (13 salvaged, 72%). The time elapsed between transplantation and FK506 conversion did not appear to influence the likelihood of success, as illustrated in Table 2.

* Abbreviations: PTLN, posttransplant lymphoproliferative disease; SCR, serum creatinine.

Preconversion immunosuppression and FK506 rescue

Prior to entry into the study, all 77 patients had been receiving CsA-steroid based immunosuppression either with (n=55) or without (n=22) azathioprine. Those patients initially immunosuppressed with triple therapy (CsA-steroids-AZA) experienced significantly greater graft salvage (45/55 patients, 82%) than those initially on double therapy (12/22 patients, 55%) after FK506 conversion ($P=0.03$). Sixty of the 77 patients (78%) had failed at least one course of OKT3 (average length of treatment 13.3 ± 6.2 days), and, of these, 27 (45%) had also received induction antilymphocyte globulin (ALG, ATG or ATGAM) (Table 3). Nineteen patients received 2 or more courses of an antilymphocyte preparation; nine patients received 3 or more. In summary, of 61 patients failing preconversion antilymphocyte preparations, 48 (79%) were salvaged with FK506. The median interval between the last dose of the antilymphocyte preparation and initiation of FK506 was 20 days (range 3 to 129 days). Although not statistically significantly different, the rate of successful conversion in patients previously treated with any antilymphocyte preparation was higher than those receiving none ($P=0.13$).

Renal function before and after FK506 rescue

As described above, 18 patients were dialysis-dependent at the time of FK506 switch: of these, 9 were successfully salvaged and became dialysis-independent. Of the remaining 59 patients not on dialysis at the time of conversion, 48 (80%) were rescued. The mean SCR prior to FK506 conversion in the successful switches was 3.2 ± 1.6 mg/dL, excluding the nine patients who were on dialysis at the time of FK506 conversion. The mean SCR after FK506 conversion was 2.25 ± 0.87 mg/dl ($P=0.002$ vs. preconversion) for those patients not on dialysis at conversion and 2.35 ± 0.97 mg/dl ($P=0.003$ vs. preconversion) for all 57 patients with functioning grafts (including the nine on dialysis at conversion), with a mean follow-up of 13.9 ± 9.1 months. Table 4 shows the time course of improvement in renal function following FK506 conversion. Overall, a statistically significant improvement in renal function was achieved within 4 weeks of conversion. For the 59 patients not on dialysis at the time of conversion, the preconversion median SCR was 3.0 mg/dl. Of 31 patients with an initial SCR ≤ 3 mg/dl, 25 (81 %) were successfully rescued compared with 23 of 29 patients (79%) with initial SCR >3 mg/dl ($P=0.85$). Hence, the quality of initial renal function did not appear to correlate directly with the likelihood of successful rescue with FK506.

Immunosuppression after FK506 rescue therapy

Prior to conversion from CsA to FK506, all patients were receiving steroid therapy. The average preconversion prednisone dose of 22.2 ± 7.2 mg/day has been lowered to 7.5 ± 5.6 mg/day, and 12 patients (21%) of the 57 with functioning grafts are currently on FK506 monotherapy (Table 5). Forty-seven of the 57 patients (82%) were also on AZA at the time of conversion. Of these, 7 have had an increase in the AZA, 24 a decrease, 16 remain on the same AZA dose, and 17 have stopped AZA (Figure 1).

Biochemical parameters after FK506 rescue

In nondiabetics, serum fasting glucose averaged 101.4 ± 20.5 mg/dl preconversion and 93.2 ± 22.0 mg/dl postconversion ($P=0.07$). Uric acid levels were 7.3 ± 2.3 mg/dl and 7.1 ± 1.5 mg/dl pre- and postconversion, respectively, ($P=0.53$). Serum cholesterol was significantly lower (207.7 ± 46.5 vs. 188.3 ± 39.7 mg/dl, $P=0.007$) postconversion. Triglycerides were 199.2 ± 101.6 mg/dl pre- and 167.2 ± 106.4 mg/dl postconversion, respectively ($P=0.06$).

Morbidity and mortality

There were six deaths, all occurring in patients whose grafts had been lost. One patient died of overwhelming sepsis 1 month following conversion to FK506: on arrival from the referring center for conversion this patient had been found to be hypotensive and in respiratory distress;

intubation was required and the patient succumbed to pneumonia within 4 weeks. In retrospect, conversion to FK506 in this patient was likely ill-advised. Two patients died of posttransplant lymphoproliferative disease (PTLD) at 1 and 7 months postconversion, respectively. In the first case, the patient also had cytomegalovirus infection. Upon review of his allograft biopsy, the diagnosis of cellular rejection was thought to have been mistaken; the patient probably had PTLD of the allograft at the time of FK506 conversion. A fourth patient died of tuberculosis 3 months following conversion. It was later discovered that this patient had been exposed to TB at the referring center prior to transfer to our institution for FK506 switch. A fifth patient died 4 months after conversion from a massive intracranial hemorrhage, and a sixth patient died following return to dialysis 8 months after failing FK506 rescue. Excluding the patients who died, nineteen patients referred to us for FK conversion had prior complications, including CMV disease in 8, urine leak requiring surgical correction in 3, ureteral obstruction in 2, perforated duodenal ulcer following high-dose steroid therapy for rejection in 1, cutaneous herpesvirus infection in 1, *Candida* esophagitis in 1, lymphocele in 1, clostridium difficile colitis in 1, and renal artery stenosis requiring transluminal angioplasty in one. Fifteen of these patients (79%) were subsequently successfully rescued with FK506. There were 16 complications following FK506 conversion including new onset diabetes mellitus in 4 patients (2 requiring insulin, 2 controlled by oral medication), CMV disease requiring ganciclovir therapy (n=3), renal artery stenosis requiring angioplasty (n=2), epistaxis (n = 1), bacterial pneumonia (n = 1), disease recurrence (membranoproliferative glomerulonephritis, n = 1), and proteinuria (n= 1). None of these complications resulted in death.

Rerejection and late failures after FK506 conversion

Two patients have required increases in immunosuppression for subsequent rejection episodes after FK506 conversion. all relatively late after rescue. One patient developed a mild rejection episode 19 months following rescue (SCR increased from 2.8 to 3.4 mg/dl) and was treated with an increase in the prednisone dose (7.5 to 15 mg/day), and continues to do well. A second patient was given a bolus steroid treatment (1 g of methylprednisolone) 3 weeks after FK506 conversion for an increase in SCR from 2.2 to 2.7 mg/dl. and continues to do well at 9.5 months of follow-up on 17.5 mg of prednisone daily (SCR 2.3 mg/dl). One patient initially thought to have been salvaged from a vascular rejection by FK506 conversion (SCR decreased from 6.4 mg/dl pre- to 2.1 mg/dl postconversion) has subsequently lost the graft and returned to dialysis 3 months following conversion.

DISCUSSION

Since its introduction in the 1980s, CsA has become the mainstay of most immunosuppressive regimens in renal transplantation. Despite the development of novel treatment strategies involving CsA, including sequential immunosuppression following antilymphocyte preparation induction and combination therapy (1–6), certain disadvantages associated with its use have persisted. The incidence of rejection episodes utilizing even multiple drug regimens based on CsA remains as high as 70% (1). Even with prophylactic antilymphocyte preparations in CsA-based regimens, steroid-resistant rejection episodes requiring additional or alternative antilymphocyte therapy occur with enough frequency and severity to often result in overimmunosuppression and/or graft loss with attendant morbidity and mortality. An alternative agent to treat recalcitrant rejection episodes that have proved resistant to steroids and/or retreatment with antilymphocyte preparations would be an important addition to the therapeutic armamentarium. Several promising “rescue” agents are currently in clinical trials, including 15-deoxyspergualin (13,14), RS-61443 (15,16), and FK506 (7,9). Phase I studies with deoxyspergualin for treatment of rejection have thus far been limited to primary rejection episodes and have thus far shown no advantage over steroids (14). The ability of deoxyspergualin to rescue grafts with steroid-resistant rejection has not yet been completely

evaluated. A preliminary report of four patients suggests that deoxyspergualin may reverse rejection in some cases (17). RS-61443 has shown promise as a potential rescue agent in a preliminary study of 72 patients with refractory rejection, of whom 55 (76%) responded (16). This experience with RS-61443 was, however, limited to first transplant recipients and no patients on dialysis were entered.

The use of FK506 as a primary agent for immunosuppression in renal transplantation has yielded graft survival rates similar to those seen with CsA, but appears to have the advantage of permitting complete steroid withdrawal in up to 60% of patients with no increased risk of rejection. The utility of FK506 as a potential rescue agent for treating ongoing rejection has been previously reported by our group in a preliminary study of 24 patients in whom graft salvage was obtained in 71% (9). In that early experience, it was determined that grafts with chronic rejection could not be salvaged by FK506. Since then, we have expanded our experience to include 77 patients with ongoing acute rejection that form the basis of the current report. Graft salvage was obtained in 74% of the cases, including 9 of 18 patients (50%) who were on dialysis at the time of conversion, 4 of 10 (40%) whose grafts had never functioned from the time of transplantation, and 48 of 61 (79%) who had received at least 1 course of an antilymphocyte preparation prior to FK506 conversion. The patient population included several risk factors—18 retransplants, 8 patients with CMV prior to rescue, and 3 patients with other infections. In the cases successfully rescued, further decreases in steroid doses were achieved in 56 (98%) and prednisone was stopped completely in 12 (21%). In only 2 cases were further increases in steroid doses necessary after conversion (1 transiently, and subsequently tapered) and only 1 patient went on to lose the graft owing to rerejection after initial salvage with FK506. The pathologic severity of initial rejection did appear to influence the likelihood of successful rescue with FK506 in that patients with cellular rejection only achieved an 85% response rate compared with 65% of those with elements of vascular rejection. In rejecting kidneys that never functioned from the time of transplantation, however, 4 of 10 could be salvaged. This, taken together with the fact that 50% of patients already on dialysis at the time of conversion achieved salvage suggests that clinical parameters of graft function may not always be a reliable guide to predicting successful reversal of rejection with FK506. In fact, there was no difference in the rate of successful rescue for patients with an initial SCR > 3 mg/dl compared with those with ≤ 3 mg/dl (excluding patients on dialysis at the time of switch). We hypothesized that another factor possibly influencing the likelihood of success was the interval between transplantation and the rescue attempt. However, we found no differences in the success rates whether FK506 conversion was performed before or after 2, 3, or 6 months following transplantation. In most cases, renal function began to improve within 4 weeks following conversion—however, in 18 of the 57 successful switches (32%), SCR actually increased within 1 week of conversion before falling to baseline levels. This is most likely due to an element of transient nephrotoxicity induced by FK506 in the early postconversion period that resolved in all cases—and, in retrospect, may have been elemental in the efficacy of the rescue process.

These data indicate that FK506 may possess a unique property as an “antirejection” drug, even though its basic mechanisms of action appear to be the same as those of CsA (18), aside from differences in potency. Properties other than inhibition of IL-2 and IL-4 synthesis (including sparing of IL-10 production in vitro) have recently been ascribed to FK506 (19). Further investigations may reveal by what mechanism FK506 may be able to reverse ongoing rejection, and these are underway in our laboratory. We are encouraged by our observations of clinical FK506 salvage therapy, and, based upon these results, an evaluation of the efficacy of FK506 as a first-line antirejection drug in direct comparison with high-dose steroid therapy appears to be indicated. It is to be hoped that, as our experience with FK506 increases, and as the results of ongoing multicenter dosing trials accumulate, the optimum use of this promising drug in clinical renal transplantation will be further elucidated.

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FIGURE 1.

Immunosuppression before and after FK506 conversion. (A) The average preconversion prednisone dose of 22.2 ± 7.2 mg/day was lowered to 7.5 ± 5.6 mg/day, with 12 patients no longer taking prednisone. (B) Of 47 patients taking azathioprine at the time of conversion (mean dose 90.0 ± 37 mg/day), 7 have had a dose increase, 24 a decrease, and 16 no change; 17 are no longer taking azathioprine. For those still taking azathioprine, the mean dose is 89 mg ± 43 mg/day. Patients 5, 16, 13, 14, 24, 25, 32, 35, 39, and 47 were not taking azathioprine before or after conversion.

TABLE 1

Outcome of FK506 conversion in 77 renal transplant patients failing primary CsA therapy

Reason for conversion to FK506	No. patients (%)	No. successfully rescued (%)
Acute cellular rejection only	47(61%)	40(85%)
Cellular + vascular rejection	20(26%)	13(65%)
Acute cellular rejection with primary nonfunction of allograft	10(13%)	4(40%)
Total	77	57(74%)

TABLE 2

Effect of timing of FK506 conversion following renal transplantation

Interval between transplantation and FK506 conversion (months)	No. patients (%)	No. Successful (%)	<i>P</i>
≤2	40 (52%)	28(70%)	0.56
>2	37 (48%)	29(78%)	
≤3	55 (71%)	40(73%)	0.90
>3	22 (29%)	17(77%)	
≤6	66 (86%)	48(73%)	0.79
>6	11 (14%)	9(82%)	

TABLE 3FK506 rescue therapy for ongoing rejection after antilymphocyte preparations^a

Type of antilymphocyte preparation	n	Graft salvage	(%)
None	16	9	56%
OKT3 only	33	26	79%
ALG only	1	1	100%
OKT3 + ALG/ATG/ATGAM	27	21	78%
Total(OKT3/ALG/ATG/ATGAM)	61	48	79% ^b

^aThe median interval between last dose of antilymphocyte preparation and FK506 conversion was 20 days.^b $P = 0.13$ compared with no antilymphocyte preparation.

TABLE 4 Renal function after conversion from CsA to FK506^a

	Time after FK506 conversion (weeks)					
	0	1	4	12	26	52
No. patients	48	48	48	43	32	20
Mean SCR (mg/dl $\pm$ SD)	3.20 $\pm$ 1.6	3.20 $\pm$ 1.9	2.57 $\pm$ 1.1	2.39 $\pm$ 0.9	2.20 $\pm$ 0.8	2.25 $\pm$ 0.9
Range	1.0–7.2	0.5–9.8	0.4–6.5	0.7–5.7	0.7–4.3	1.1–4.7
<i>P</i> (vs. time 0)	NA ^b	0.90	0.003	0.003	0.004	0.002
Mean BUN (mg/dl $\pm$ SD)	52.2 $\pm$ 31.0	55.4 $\pm$ 33.5	42.0 $\pm$ 20.8	40.4 $\pm$ 18.6	35.8 $\pm$ 13.2	35.3 $\pm$ 14.8
Range	12–154	14–149	11–116	19–91	16–58	16–57
<i>P</i> (vs. time 0)	NA	0.1	0.05	0.03	0.01	0.03

^aExcluding patients on dialysis at the time of conversion to FK506.^bNA: not applicable.

TABLE 5

Prednisone dose before and after FK506 rescue

Prednisone dose(mg/day)	No. patients (%)	
	Preconversion	Postconversion
0	0 (0%)	12 (21%)
1.25–2.5	0 (0%)	4(7%)
5	0 (0%)	8(14%)
7.5	0 (0%)	5(9%)
10	5 (9%)	14 (25%)
12.5	1 (2%)	6 (10%)
15	3 (5%)	6 (10%)
20	29 (51%)	1 (2%)
>20	19 (33%)	1(2%)
Mean dose	22.2 ± 7.2	7.5 ± 5.6