Long Term Outcome of Renal Allografts in Patients with Immunoglobulin A Nephropathy

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SUMMARY

Recurrent glomerular disease is an important cause of late allograft loss in renal transplant recipients. Immunoglobulin A nephropathy (IgAN) is a leading cause of end-stage renal disease (ESRD) worldwide and its recurrence has been reported in allografts. The present study examined outcomes following renal transplantation (RTX) in 101 patients with ESRD due to biopsy-proven IgAN, in comparison to non-IgA patients, and evaluated the incidence of recurrence. The study population (mean age 34.8 ± 7.7 years; males 62.2%; Chinese 88.3%) underwent RTX under CsA immunosuppression between November 1984 and December 2004; as two patients underwent re-transplantation during the study period, 103 allografts (56.3% cadaveric) were included for retrospective analysis. At time of analysis on 1 January 2005, 78 (75.7%) renal allografts (IgAN RTX) were functioning, of which 51 (49.5%) had normal serum creatinine, 27 (26.2%) had chronic allograft dysfunction, while 25 had graft losses, either due to patient death with functioning grafts (5.8%) or withdrawal to dialysis (18.5%). Persistent microscopic haematuria, not attributable to other causes or proteinuria > 1 g/day occurred in 42.7% and 13.6% of allografts respectively. Of 29 allografts biopsied for evaluation of proteinuria and/or renal dysfunction post-RTX, 8 (27.6%) had IgAN (overall histological recurrence, 7.8%). Of these, three had graft loss due to recurrent IgAN, three had elevated serum creatinine, while two had normal serum creatinine. Overall five and ten year patient survivals for IgAN RTX were 95.3% and 82.2%, and five and ten year actuarial graft survivals were 82.3% and 67.8% respectively. Five and ten year patient and graft survivals for IgAN RTX were not significantly different from that for non-IgAN RTX. In summary, RTX patients with IgAN have a low incidence of documented histological recurrence and recurrence contributing to graft loss occurs in only 2.9%. These results suggest that RTX is an excellent modality of renal replacement therapy in this population.

KEY WORDS:
Histological recurrence, Renal biopsy, Cyclosporine, Survivals

INTRODUCTION

Renal allotransplantation (RTX) is the ideal form of renal replacement therapy for patients with end-stage renal disease (ESRD). Nevertheless, late complications such as recurrence of the original renal disease, is an important cause of late graft loss. Hariharan *et al*, for the Renal Allograft Disease Registry documented a 2.8% incidence of recurrent disease at two years post-RTX with the incidence increasing to 9.8% and 18.5% at five and eight years respectively, post-RTX [1]. They further documented that recurrence of original disease in renal allografts contributes significantly to late renal allograft dysfunction and graft loss. Thus evaluation of recurrence and its implications to allograft function is of clinical importance.

Among the glomerulonephritides, IgA nephropathy (IgAN) is the most common primary glomerulonephritis (GN) worldwide and contributes to 30 to 50% of primary GN in Asia[2,3]. In Singapore, IgAN is the most common form of GN accounting for 45% of all the primary GN [3]. As, in addition, IgAN is the leading cause of GN resulting in ESRD in Singapore[4], its recurrence post-RTX may contribute to significant allograft dysfunction and would be of relevance.

Currently available data from small series suggests a wide variation in the incidence of recurrent IgAN in renal allografts with a range of 9% to 75%[5-8]. In addition, the natural history of IgAN in renal allografts has not been fully elucidated. Some series report an indolent course for the recurrent disease[9] while others have observed a more aggressive and/or unfavourable outcome[10,11]. The present study examined the clinical course post-RTX under Cyclosporine immunosuppression for patients with ESRD due to biopsy-proven IgAN, the incidence of recurrent IgAN and compared overall graft and patient survivals in these patients to that of a control population with non-IgAN induced ESRD.

MATERIALS AND METHODS

Transplant case records of all patients on follow-up at the Singapore General Hospital (SGH) who had undergone RTX between November 1984 and December 2004 under Cyclosporine-based immunosuppression were reviewed. One hundred and one patients with ESRD due to biopsy-proven IgAN in their native kidneys were identified; two of these patients had undergone re-transplantation and altogether 103 renal allografts were included in the retrospective analysis. The study population included recipients undergoing cadaveric RTX at SGH (CRTX) and recipients receiving cadaveric transplants from China (CCRTX), as well as living-related (LRTX) recipients performed at SGH and living-unrelated RTX (LNRTX); the latter included spousal RTX performed at SGH and commercial RTX from India. All

This article was accepted: 10 April 2007
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patients were on Cyclosporine-based (CsA) therapy with corticosteroids as previously described [12]. Dual therapy with CsA and steroids was the immunosuppression for 18 grafts; 83 RTX received Azathioprine (Aza) as part of a triple drug regimen as previously described [12], while 2 RTX transplanted since the year 2000 received Mycophenolate Mofetil (MMF) as the third immunosuppressant.

The 103 IgAN RTX were evaluated for presence or absence of microscopic haematuria, proteinuria, degree of proteinuria, serum creatinine and functional graft status (functioning grafts or graft loss). For those who had renal allograft biopsy, the indications for biopsy and histology of the biopsy were reviewed. Recurrent IgAN was diagnosed only when the histology of the allograft biopsy and that of the native kidney were documented as IgAN. The pre-transplant clinical and histological characteristics and outcome of allografts with histological recurrence were analyzed and compared with that of IgAN patients without recurrence.

Overall actuarial graft and patient survivals of the study population were calculated by Kaplan Meier analysis; comparisons between groups were made by log rank analysis. Graft loss was defined as return to dialysis; patients who died with a functioning graft were censored at time of death for analysis of graft survival. Patients with graft loss were censored at six months after graft loss for analysis of patient survival. Graft and patient survivals were compared by log rank analysis for IgAN RTX stratified by type of transplant (LRTX vs. CRTX), those on dual vs. triple therapy with Aza and for those with and without haematuria or proteinuria. Demographic characteristics and graft and patient survivals were also compared between the study population and a control population. The control population comprised of LRTX and CRTX (n= 94 and 416 respectively) with ESRD due to diseases other than IgAN, matched for interval post-RTX, transplanted at SGH; these patients were compared with IgAN LRTX and CRTX transplanted at SGH. Overseas CCRTX and LNRTX were excluded from this analysis so as to avoid bias from overestimating their survival, as only those with successful RTX would return to our transplant centre for follow-up. All statistical analyses were performed using the SPPS statistical package for Windows; both parametric and non-parametric tests were used as indicated.

RESULTS

The study population comprised of predominately cadaveric grafts (56.3%), of which 53 were CRTX and five were CCRTX; the remainder were LRTX and LNRTX in almost equal proportions (22 and 23 RTX respectively). The mean age of the study population at time of RTX was 34.8 ± 7.7 years, with 62.2% male. The racial distribution was similar to that of the population of Singapore, with predominately Chinese (88.3%), while Malays and Indians constituted 7.7% and 4.0%, respectively. The mean interval from ESRD to renal transplantation was 2.2 ± 2.3 years and patients had been followed up at SGH post-RTX for a mean interval of 8.7 ± 3.7 years.

Five and 10-year actuarial patient survivals for the study population were 95.3% and 82.2%, respectively, while the 5 and 10-year actuarial graft survivals were 82.3% and 67.8%, respectively (Figure 1). There were no significant differences in graft and patient survivals of LRTX versus CRTX with IgAN undergoing transplantation at SGH. Overall, as of 1 January 2005, 78 IgAN RTX (75.7%) were functioning, of which 51 (49.5%) had normal serum creatinine (normal range at our institution: 41- 141 mmol/L) while 27 (26.2%) had abnormal allograft function with mean serum creatinine of 191.4 mmol/l. There were 25 IgAN RTX (24.3%) that were lost either as a result of graft failure (19 allografts or 18.5%) or patient deaths with functioning grafts (six allografts or 5.8%). Seven of these graft losses were due to primary non-function and/or early vascular rejection, seven were due to chronic rejection, three were due to recurrent IgAN, while two patients had chronic allograft dysfunction with proteinuria and were not biopsied due to patient refusal.

Evaluation for presence of microscopic haematuria and/or proteinuria in the IgAN RTX population revealed a high incidence of urinary abnormalities. Microscopic haematuria, not attributable to other causes, with increased dysmorphic red blood cells was observed on two or more occasions in 44 IgAN RTX (42.7%). There were no differences in graft survival between those with or without microscopic haematuria, in the absence of proteinuria. Forty-one RTX (39.8%) had proteinuria > 150 mg/day at some time post RTX follow-up. Proteinuria ranged from 0.20 g/day to 11.13 g/day; in the vast majority, proteinuria remitted or remained < 1 g/day over the course of follow-up and persistent proteinuria > 1 g/day was documented in only 13.6% of IgAN RTX (14 of 103).

Allograft biopsies were performed in 29 IgAN RTX (28.2%) at a median interval of 2.2 months post RTX for the following indications: rising serum creatinine in 18 (17.5%), proteinuria >1 g/day in 5 (4.9%), and rising serum creatinine and proteinuria >1 g/day in 6 (5.8%). Of those undergoing allograft biopsy, eight were found to have recurrent IgAN, giving rise to an overall histological recurrence of 7.8% (recurrence rate of 27.6% in biopsied patients). Other histology included acute rejection in 12 (11.7%), CsA nephrotoxicity in 3 (2.9%), chronic rejection in 3 (2.9%), acute tubular necrosis in 2 (1.9%) and focal segmental glomerulosclerosis in 1 (1.0%).

On stratification of RTX by immunosuppression used, histological recurrence was not significantly different between those receiving dual therapy (recurrent IgAN in 1 of 18, 5.6%) versus those receiving triple therapy with Aza (7 of 83, 8.4%). The number of RTX receiving MMF as initial immunosuppression was too few for meaningful analysis for recurrent IgAN. Of the 8 IgAN RTX with histologically-proven recurrence, three had undergone cadaveric RTX, three were LRTX and two were LNRTX. Three IgAN RTX were lost due to recurrent IgAN (mean duration to graft loss was 4.6 years); three had raised serum creatinine with mean serum creatinine 208 mmol/l and two had normal serum creatinine. There was a trend to lower graft survival for RTX with recurrent IgAN: 10-year survival of 44.4% in IgAN RTX with recurrence versus 85.7% in IgAN RTX without recurrence (p=0.88). However, this difference did not reach significance likely because of the small numbers. The time course to renal manifestations of recurrent IgAN in these eight patients (Table I) illustrates that microscopic hematuria generally precedes onset of proteinuria in RTX with recurrent IgAN.

There were no significant differences in pre-transplant characteristics of IgAN RTX patients with and without histological recurrence (Table II). Finally, overall actuarial graft and patient survivals of LRTX and CRTX were comparable between IgAN and non-IgAN (Table III).

Table I: Clinical Course of Renal Abnormaliities in Renal Transplant Recipients With Recurrent IgA Nephropathy (N=8)

	No of Patients	Interval to Onset (years) [1]
Microscopic Haematuria	7	2.5 ± 2.1
Proteinuria		
< 1 g/day	1	
1-3 g/day	2	2.6 ± 0.4
> 3 g/day	4	
Allograft Biopsy [2]	8	2.8 ± 2.0

[1] Mean ± Standard deviations are reported.
[2] One patient without proteinuria and haematuria was biopsied for rising serum creatinine and was found to have IgAN.

Table II: Impact of Pre-Transplant Characteristics on Histological Recurrence in Renal Transplant Recipients With IgA Nephropathy

	Recurrent IgAN (N=8)	No Recurrence (N=21)	P Value
Time to ESRD (years)[1]	4.2 ± 3.1	4.0 ± 3.5	0.70
Duration of Dialysis (years) [2]	2.4 ± 3.6	2.8 ± 2.3	0.89
Peak Proteinuria Pre- Renal Transplantation	1.6 ± 0.9	2.6 ± 2.0	0.19
% Glomeruli with Cellular Crescents	3.1 ± 6.2	4.6 ± 6.6	0.60
% Glomeruli with Sclerosis	45.2 ± 27.9	52.6 ± 30.2	0.60

[1] Calculated as interval from native renal biopsy to dialysis. Mean ± Standard deviations are reported.
[2] Mean ± Standard deviations are reported.

Table III: Actuarial Patient and Graft Survivals: IgA Nephropathy Versus Non-IgA Nephropathy[1]

	Living-Related					
	Graft			Patient		
	IgA (N=22)	Non IgA (N=94)	P Value	IgA (N=22)	Non IgA (N=94)	P Value
5 year Survival	84.4%	92.9%	0.77	88.9%	100%	0.46
10 year Survival	76.0%	84.4%		88.9%	98.3%	
	Cadaveric					
	Graft			Patient		
	IgA (N=53)	Non IgA (N=416)	P Value	IgA (N=53)	Non IgA (N=416)	P Value
5 year Survival	85.0%	79.6%	0.21	95.2%	91.9%	0.35
10 year Survival	75.7%	63.2%		90.4%	83.4%	

[1]Actuarial graft and patient survivals were compared by log rank analysis of Kaplan Meier survival curves.

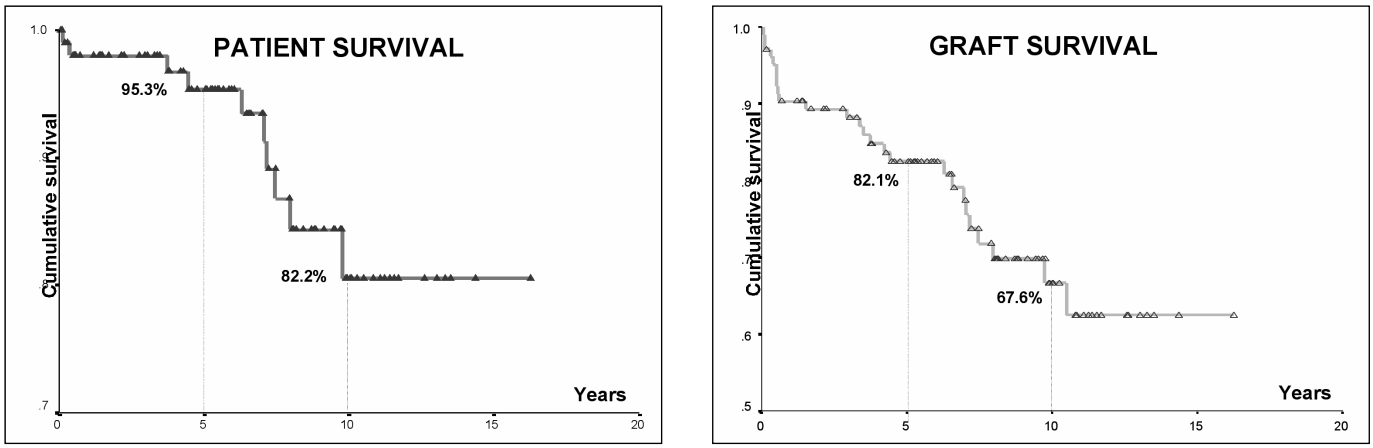

Fig. 1: Actuarial Graft and Patient Survival in Renal Transplant Recipients with IgA Nephropathy

DISCUSSION

Recurrent renal disease has been reported to be a significant problem after RTX and has been suggested to be an important cause of late graft loss. The present study clearly demonstrated that only a small percentage of patients with ESRD due to biopsy proven IgAN, namely 7.8%, had histologically proven recurrent IgAN over a mean interval of follow-up of 8.7 years post-RTX.

The rate of recurrent IgAN in the transplant kidneys as reported herein is lower than that reported from other series. On the one hand, the lower incidence of recurrence in our series may be attributed to the higher threshold for allograft biopsy in our series. Microscopic haematuria per se, with or without proteinuria, was an indication for allograft biopsy in the study reported by Wang *et al*, indicating a much lower threshold for diagnosis of recurrent IgAN in their study population[13]. However, the significance of microscopic haematuria alone in this setting is unclear, as it is difficult to ascertain if the haematuria is from the native or transplant kidneys; other de novo glomerulonephritides could also be associated with increased urinary dysmorphic red blood cells. Allograft biopsies were performed in our series for persistent proteinuria > 1 g/day, or for allograft dysfunction with or without proteinuria. Indeed, persistent proteinuria > 1 g/day is the hallmark of clinically significant IgAN in native kidneys and is the criterion used for native and transplant renal biopsy in SGH[3,14]. Nevertheless, as all patients with microscopic hematuria alone or those with proteinuria < 1 g/day or remitting proteinuria were not biopsied, it can be argued that many other patients had undiagnosed recurrent IgAN. Likewise, the incidence of histological recurrence could become higher with longer duration of follow-up.

On the other hand, recurrence may be lower in our series due to the type of immunosuppression used; our analysis is of patients receiving CsA-based immunosuppression. An earlier series of patients reported by Odum *et al* documented a 60% incidence in 51 patients with IgAN; this series included Aza and/or CsA-treated RTX transplanted between 1977 and 1992[7]. Bumgardner *et al* likewise reported a 29.5% incidence of recurrence in 61 population treated with Aza and/or CsA transplanted between 1980 and 1994[15]. Andresottir *et al* reported histological recurrence of 53% but clinical recurrence of 9% in 79 IgA RTX receiving Aza and / or CsA therapy[8]. Tomlanovich *et al* have suggested that CsA, through immunological mechanisms may abrogate the incidence of recurrent IgAN[16]; nevertheless, other studies have not supported this conclusion. For example, Kessler *et al*, in a study in 84 RTX with IgAN and Henoch-Schonlein nephropathy receiving CsA immunosuppression, reported a 46.4% incidence of recurrent disease[17]. Wang *et al* in a series of 48 IgAN RTX receiving CsA-based immunosuppression reported recurrence in 29% of their patients over a median duration of follow-up of 52 months[13]. The lower incidence of recurrence as reported herein from our larger study would support the hypothesis that CsA-based immunosuppression could potentially mitigate the recurrence of IgAN post-RTX. KN Lai *et al* have demonstrated reduction in proteinuria in patients with native IgAN[18], treated with CsA, further supporting the hypothesis that immunosuppression may have an impact on recurrent glomerular disease.

Our results demonstrated overall excellent long-term patient and graft survivals in IgAN RTX, comparable to those of patients with non-IgA diseases. There has been considerable debate on the impact of the native IgAN on outcomes post RTX; incidence of graft loss varying from 5.7% to 21.4% have been reported [6, 7, 13, 16, 19]. Lim and Terasaki, for the UNOS database, reported higher survival rate for IgAN RTX than for other primary diseases [20]. They suggested a protective effect of IgA anti-HLA antibodies in RTX with IgAN. Indeed, Lim et al demonstrated in vitro that IgAN RTX with IgA antibodies to HLA had a 100% two year cadaveric graft survival rate compared with 70% in those without IgA antibodies[21]. On the other hand, Ohmacht C *et al* attributed worse graft outcomes in IgAN RTX mainly due to recurrence of original disease[19]. Overall graft outcomes in patients with IgAN in our series were excellent due to the low incidence of recurrent IgAN (graft loss due to recurrent IgAN was 2.9% in our series). Nevertheless, graft survival was lower in IgAN RTX with recurrence, with ten year survival of 44.4% in those with recurrence versus 85.7% in those without recurrence.

Some studies have suggested a higher incidence of recurrent IgAN and a trend toward more allograft dysfunction among living-related allografts[17,22]. Not withstanding the overall low incidence of recurrence in our study population, there were no significant differences in rates of recurrence between LRTX and CRTX IgAN (recurrence occurred in 5.2% of the cadaveric allografts and 13.6% of the living-related allografts; p = NS). Of note however was that of the three IgAN LRTX with recurrence, two patients were recipients of HLA identical kidneys from their siblings. Genetic susceptibility particularly association with certain HLA antigens (HLAB35 and DR4), has been suggested by some authors [6, 22], an association that was not evident in our series. Though Wang *et al* suggested a protective effect of HLAA2, a very common histocompatibility antigen in our Asian population, on recurrence in their series, its presence in our study population did not apparently confer protection. Nevertheless, the apparent predominance of recipients of HLA identical kidneys among those with recurrence suggests that some immunological mechanisms, hitherto undefined, may play a role in recurrence of the disease.

Post transplant proteinuria, generally occurring at 2.6 years post-RTX was almost invariably present in all patients with recurrence; those with recurrence and graft loss had nephrotic range proteinuria (3.8, 4.5, 11.1 g/day). Of interest was that microscopic haematuria per se was not an adverse risk factor for recurrent IgAN. These findings are similar to that of the native renal disease as asymptomatic haematuria in the absence of proteinuria in native IgAN is associated with a benign course[14].

CONCLUSION

In summary, our results from the largest series of IgAN RTX hitherto reported, all receiving CsA immunosuppression, demonstrated a low histological recurrence rate of 7.8% and recurrence contributing to graft loss occurred in only 2.9% of the allografts. However, once histological recurrence was documented, the long-term allograft prognosis was unfavourable, as graft loss occurred in patients with

recurrence at a mean interval of 4.6 years post-RTX. Nevertheless, such a low overall incidence of graft loss due to recurrent IgAN suggests that renal transplantation is an excellent modality of renal replacement therapy in patients with IgAN. Cyclosporine immunosuppression may ameliorate progression of renal disease in IgAN and warrants further exploration.

REFERENCES

1. Hariharan S, Peddi VR, Savin VJ *et al*. Recurrent and de novo renal diseases after renal transplantation: A report from the renal allograft disease registry. Am J Kidney Dis 1998; 31: 928.
2. G D'Amico. Epidemiological, clinical and prognostic indices in IgA nephropathy. Nephrology 1997; 3: 13.
3. Woo KT, Chiang GSC. Glomerulonephritis in Singapore (1987-1997). Medicine of the Americas 2000; 1: 30.
4. Woo KT, Chiang GS, Pall A, Tan PH, Chin YM. The changing pattern of glomerulonephritis in Singapore over the past two decades. Clin Nephrol 1999; 52: 96.
5. Berger J, Noel LH, Nabarra B. Recurrence of mesangial IgA nephropathy after renal transplantation. Contr Nephrol 1984; 40: 195.
6. Bachman U, Biava C, Amend W, *et al*. The clinical course of IgA nephropathy and Henoch-Schonlein purpura following renal transplantation. Transplantation 1986; 42: 511.
7. Odum J, Peh CA, Clarkson AR *et al*. Recurrent mesangial IgA nephritis following renal transplantation. Nephrol Dial Transplant 1994; 9: 309.
8. Andresdottir MB, Hoitsma AJ, Assmann KJM, Wetzels JFM. Favorable outcome of renal transplantation in patients with IgA nephropathy. Clinical Nephrology 2001; 56: 279.
9. Kotanko P, Pusey CD, Levy JB. Recurrent glomerulonephritis following renal transplantation. Transplantation 1997; 63: 1045.
10. Floege J, Burg M, Klien V. Recurrent IgA nephropathy after kidney transplantation: not a benign condition. Nephrol Dial Transplant 1998; 13: 1933.
11. Frohnert PP, Donadio JV Jr, Velosa JA, Holley KE, Sterioff S. The fate of renal transplants in patients with IgA nephropathy. Clin Transplant 1997; 11: 127.
12. Vathsala A, Woo KT. Renal transplantation in cyclosporine-treated recipients at the Singapore General Hospital. Clinical Transplants 1999, Cecka and Terasaki eds. UCLA Immunogenetics Center, Los Angeles, California. 189.
13. Wang AY, Lai FM, Yu AW *et al*. Recurrent IgA nephropathy in renal transplant allografts. Am J Kidney Dis 2001; 38: 588.
14. Woo KT, Edmondson RP, Wu AY, Chiang GS, Pwee HS, Lim CH. The natural history of IgA nephritis in Singapore. Clin Nephrol 1986; 25: 15.
15. Bumgardner GL, Amend WC, Ascher NL, Vincenti FG. Single-center long-term results of renal transplantation for IgA nephropathy. Transplantation 1998; 65: 1053.
16. Tomlanovich S, Vincenti F, Amend W *et al*. Is cyclosporine effective in preventing recurrence of immune-mediated glomerular disease after renal transplantation? Transplant Proc 1988; 20: 285.
17. Kessler M, Hiesse C, Hestin D, Mayeux D, Boubenider K, Charpentier B. Recurrence of immunoglobulin A nephropathy after renal transplantation in the cyclosporin era. Am J Kidney Dis 1996; 28: 99.
18. Lai KN, Lai FM, Li PK, Vallance-Owen J. Cyclosporine treatment of IgA nephropathy: a short term controlled study. Br Med J (Clin Res Ed) 1987; 295: 1165.
19. Ohmacht C, Kliem V, Burg M *et al*. Recurrent immunoglobulin A nephropathy after renal transplantation: a significant contributor to graft loss. Transplantation 1997; 64: 1493.
20. Lim EC, Terasaki PI. High survival rate of kidney transplants in IgA nephropathy patients. Clin Transplants 1992; 6: 100.
21. Lim EC, Chia D, Gjertson DW, Prasad K, Terasaki PI. In vitro studies to explain high renal allograft survival in IgA nephropathy patients. Transplantation 1993; 55: 996.
22. Brensilver JM, Mallat S, Sholes J, McCabe R. Recurrent IgA nephropathy in living-related donor transplantation: Recurrence or transmission of familial disease? Am J Kidney Dis 1988; 12: 147.