Transition to the adult nephrologist does not induce acute renal transplant rejection

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Abstract

Background. In spite of the overall increased renal graft survival, long-term allograft survival has remained least successful in adolescent recipients. A major change in their care is the transition from the pediatric to the adult nephrology unit.

Methods. To analyse the effect of transition on the acute rejection frequency and graft survival, we performed a historical cohort study in all patients transplanted at the pediatric unit between 1980 and 2004. Data were obtained by reviewing medical charts in two of the four Dutch pediatric renal transplantation centers from time of transplantation until 3 years after transition. For analysis, we used a Cox proportional hazards model.

Results. The cohort consisted of 162 patients: 133 native Dutch and 29 immigrant patients. Transition occurred at a mean age of 18 years (range 14–22). At transition, 72% had a functioning allograft. Acute rejections occurred in 92/162 patients before (median follow-up 4.8 years, range 0.2–12.8) and in 15/116 patients after transition (median follow-up 3.0 years, range 1.6–3.0). Most rejections (62%) occurred within the first year after transplantation. The relative risk of acute rejections after transition in comparison to before transition was 0.10 [95% confidence interval (95% CI) 0.04–0.28] in Dutch patients and 0.69 (95% CI 0.33–1.40) in immigrant patients. In the 3 years before transition, 28/154 patients (18%) experienced graft failure compared to 19/116 patients (16%) in the 3 years after transition.

Conclusions. The risk for acute rejection decreases after transition to the adult unit. There is less risk reduction in immigrant patients. Nephrologists should pay special attention to these patients.

Keywords: adolescence; non-adherence; renal transplantation; transition

Introduction

Renal transplantation has been the first modality of choice since the introduction of chronic renal replacement therapy in children in the late 1960s. Yet, for a long time, graft survival rates in children were significantly lower than in adults, especially in very young children and in adolescents. This picture has changed over the last 15 years. Graft survival rates, particularly of the very young recipients, have significantly improved [1–3]. However, in spite of the overall increased graft survival, long-term allograft survival has remained least successful in adolescent recipients [1]. According to the data of the United Network for Organ Sharing, the renal mean allograft half-life for adolescents is 7 years, as compared to 11 years for adults and younger children [1].

Acute rejection and graft loss have been linked to age-dependent non-adherence to medical prescriptions [5,14, 15]. Estimates of non-adherence with immunosuppressive medication in pediatric renal transplant recipients range from 5 to 70%, with adolescents accounting for the highest percentage [16]. Adolescent renal transplant recipients have therefore been recognized as a high-risk group for unsuccessful long-term allograft survival [1,17–19].

Acute rejection has been shown to have a great impact on overall graft survival in adolescents. In addition to the acute threat of loss of the allograft, acute rejection episodes (ARE) markedly increase the risk of developing chronic rejection, thereby enhancing possible allograft loss over time. In a study of 7123 children, it was found that a late initial rejection (>365 days post-transplant) increased the risk of chronic rejection graft failure 3.6-fold, while a second acute rejection resulted in a further 4.2-fold increase [4]. Given this association, the prevention of ARE is extremely important in long-term graft survival.

One of the major changes in the care for this high-risk group of adolescent patients is the transition to the adult nephrologists. Decades ago, the transition to adult health care for children with complex medical conditions was rarely an
issue since only a few of these children survived into adulthood. Nowadays, the development of a proper transitional care has become a major challenge for paediatric and adult providers alike. Eight years ago, Watson published a paper demonstrating the adverse effect of transition on graft survival [5]. In a historical cohort study following 20 patients with a functioning renal transplant after transition to adult care, seven transplants were found to fail unexpectedly within 36 months. Since then, it is believed among paediatric nephrologists that transition to adult health care for adolescents is indeed an important risk factor for increased graft loss due to medication non-adherence. Yet, despite the internationally growing interest in transitional care of young adults to the adult system, the findings of Watson et al. have never been replicated in a large cohort.

In the Netherlands, a considerable proportion of children with end-stage renal disease are from immigrant families. It is known that, in general, immigrants receive less appropriate health care than indigenous patients [6]. For example, ethnicity and insufficient comprehension of the Dutch language have been found to influence asthma control in children and adolescents [7].

The aim of this study was, therefore, to evaluate the effect of transition on the occurrence of ARE and graft failure in a large and complete cohort of patients, and to investigate whether this transition effect differed between patients from Dutch origin and immigrant patients.

Materials and methods

Study design

The study was designed as a historical cohort study. The period of observation for the analysis of acute rejections ranged from the last transplantation prior to transition until a maximum of 3 years after transition or until graft failure. In the case of graft failure, either before or after transition, the end of the follow-up was indicated by the date of starting dialysis or re-transplantation; in case of a functioning graft, follow-up was continued until 2007.

Patients

The study was performed in the paediatric nephrology centers of Emma Children’s Hospital in Amsterdam (Academic Medical Center, AMC) and St Radboud Hospital in Nijmegen (University Medical Center Nijmegen, UMCN). Eligible patients were identified by the Dutch Registry on Transplantations (NOTR, Leiden, The Netherlands). We checked the accuracy of data on these patients by comparing NOTR data with the databases of the two Dutch centers for paediatric kidney transplantation and with the databases of the centres for adult transplantation. Transition was defined as the date of the patient’s first appointment at the adult unit. In the Netherlands, transition from the paediatric to the adult nephrology unit officially takes place at the age of 18 years. Therefore, the cohort comprised all patients from these two centres who had had one or more transplantations between 1980 and 2004 before the age of 18 years. Some patients transferred for adult care to other hospitals, but annual updates of all patients were collected in the adult medical centres of the AMC and UMCN. Information about graft failure was available through the NOTR until 2007. In order to provide a follow-up of acute rejection episodes for at least 3 years after transition, we excluded patients who were born after 1986.

Data collection

Data were collected from hospital databases and by reviewing the paediatric and adult medical charts by a single observer (M.H.), and discussed with experienced nephrology consultants (A.B., F.B., E.C., A.H.) whenever clarification was necessary. Quality checks were performed at random by a second researcher (J.G.). The following information was extracted from the medical charts: ethnicity, primary renal disease, information about the last transplantation prior to transition (date, age, donor source, first transplant or re-transplant), date and cause of graft failure, information about acute rejection episodes (date, biopsy, immunosuppressive therapy at the time of the rejection episode, ciclosporine/tacrolimus levels if applicable, note of suspicion for non-adherence by the physician, rejection therapy or was confirmed as acute rejection by renal biopsy. The date of graft failure was defined as the day of onset of chronic dialysis or the date of a new transplantation. Chronic rejection was defined as a gradual but progressive deterioration of graft function leading to dialysis in the absence of other specific causes. Chronic rejections were diagnosed by biopsy or, in the case that no biopsy had been performed, by a gradual rise of serum creatinine with exclusion of other possible causes of graft dysfunction, such as cyclosporine toxicity or cytomegalovirus infection, as noted in the medical chart.

Statistical analysis

The effect of transition was investigated by a model in which the hazard of the end point of interest was regressed on transition as a time-dependent covariate. We included age, ethnicity, centre, calendar period, donor source and gender in the regression model in order to correct for possible confounders and to investigate the presence of effect modifiers. The model tested interaction effects between age and ethnicity, and between transition and the variables ethnicity, gender, centre and calendar period.

We investigated the risk of ARE in a Cox proportional hazards model with time since transplantation as the principal time scale. However, we corrected for the effect of the previous ARE by including time since previous ARE as covariate in the model. Therefore, patients before and after transition were compared, who were at the same time since transplantation and at the same time since the previous ARE. A further correction was made for repeated AREs by including a random effect term: each patient was supposed to have an unobserved ‘proneness’ to experience subsequent AREs [8,9].

For graft failure, a standard Cox proportional hazards model was used. Patients before and after transition, who were at the same time since transplantation, were compared with respect to the risk of graft failure. There were four patients with graft loss at the date of transition. For these patients, no follow-up time was contributed to the period after transition. We used R 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria). P-values and confidence intervals were obtained using univariate and multivariate Wald tests.

All descriptive statistical analyses were performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). P-values <0.05 were considered statistically significant.

Results

Descriptives

Patient characteristics. The cohort consisted of 162 patients: 44 from the AMC and 118 patients from the UMCN. The main characteristics of the cohort are given in Table 1. The number of immigrant patients was 29 (18%). There was a difference in ethnic background of the patients in the two hospitals: 28 patients (64%) from the AMC population were of Dutch origin in comparison to 105 patients (89%) from the UMCN population. The last transplantation before transition had been performed at a median age of 13 (range 4–18) years. The median age at transition was 18 (range 14–22) years. At the time of transition, 116 patients (72%) had a functioning allograft. The median age of death of the 13 deceased patients was 13 years (range 7–21). Figure 1 shows the Kaplan–Meier survival curve for patient and graft survival per center.
Acute rejection episodes. There were 195 ARE. One or more ARE occurred in 101 (62%) patients: in 76 (57%) of the Dutch patients and in 25 (86%) of the immigrant patients. This is shown in Figure 2, where each line corresponds with a single patient and his/her course over time (years) since transplantation. The number of acute rejection episodes per patient was 1 in 45 patients, 2 in 34 patients, 3 in 10 patients, 4 in 8 patients and 5, 6 and 7 in one patient each. The median time from transplantation until the first ARE was 0.3 (range 0.1–17.4) years. ARE tended to cluster together: 62% of the subsequent rejections occurred within 1 year after the transplantation. There were 121 ARE during the first year after transplantation (148 person-years of follow-up) and 72 ARE after that first year (928 person-years of follow-up). There were 153 ARE in the 116 first transplants (1092 person-years of follow-up) in comparison with 42 ARE in the 46 re-transplants (432 person-years of follow-up). Acute rejections occurred in 92/162 patients (57%) before transition [median follow-up period 4.8 (range 0.2–12.8) years] and in 15/116 patients (13%) after transition [median follow-up period 3.0 (range 1.6–3.0) years]. There were 70 ARE in the period of 3 years prior to transition (362 person-years of follow-up) and only 17 ARE in the period of 3 years after transition (422 person-years of follow-up).

Graft failure. In the cohort of 162 patients who received a renal transplantation between the age of 4 and 18 years, 63 patients (39%) lost their graft before the age of 21 years. Their median transplant survival until graft failure was 3 (range 0–15) years. Within 1 month after transplantation, two patients died and five other patients had renal graft failure. Five patients died in spite of a functioning renal graft after a median period of 6.0 (range 0–12) years post-transplantation. Graft failure before the age of 21 years occurred at a median age of 16 (range 7–21) years. In 34 out of 63 cases, graft failure was preceded by chronic rejection; this was proven by biopsy in 26 (77%) cases. For Dutch patients and immigrant patients, the occurrence of chronic rejection was 34% and 41%, respectively. In 3 years prior to transition, 28/154 patients (18%) experienced graft failure compared to 19/116 patients (16%) in the 3 years after transition.

**Table 1. Characteristics of the study population**

<table>
<thead>
<tr>
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<th>%</th>
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<tbody>
<tr>
<td>Number of patients (female)</td>
<td>162 (72)</td>
<td>100 (44)</td>
</tr>
<tr>
<td>Primary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulopathy</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Secondary glomerulonephritis</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Uropathy</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Congenital disorders</td>
<td>58</td>
<td>36</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch (UMCN)</td>
<td>133 (105)</td>
<td>82 (89)</td>
</tr>
<tr>
<td>European (minus Dutch)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>African</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>South American</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Median age at transplantation, years [range]</td>
<td>13 [4–18]</td>
<td></td>
</tr>
<tr>
<td>Number of transplantations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>116</td>
<td>71</td>
</tr>
<tr>
<td>Second</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Third</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Donor source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-mortem</td>
<td>135</td>
<td>83</td>
</tr>
<tr>
<td>Living related</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Median age at transition, years [range]</td>
<td>18 [14–22]</td>
<td></td>
</tr>
<tr>
<td>Number of deaths (before transition)</td>
<td>13 (10)</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

*German (3), Portuguese (1), Albanese (1), Turkish (9), Polish (2), Russian (1); Moroccan (2), South African (1); Surinamese (2), Colombian (1), Antillean (2); Iranian (2), Pakistani (2).

**Fig. 1.** Patient and graft survival of the study population per center.

**Fig. 2.** Summary of rejection data per patient from date of transplantation.
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Overall effect of transition ($P = 0.06$). There was a significant interaction effect between ethnicity and transition ($P = 0.01$). The HR for chronic rejection in Dutch patients after transition compared with before transition was 0.14 (95% CI 0.037–0.52). For the immigrant patients, the HR was 2.8 (95% CI 0.45–17).

Estimation of GFR

Transition and successive creatinine values. We calculated the slope of the trend line of the successive serum creatinine values per patient as an indication for the GFR of the renal allograft using a random effects model. We analysed these slopes by comparing the trend line of all patients before transition with the trend line of the patients after transition. We found no significant difference in the estimate of the graft function before and after transition ($P = 0.193$).

Discussion

We found no increase in ARE after transition from the paediatric to the adult nephrology unit in adolescent renal transplant recipients. On the contrary, we found that the risk of ARE in Dutch patients was significantly reduced in the 3 years after transition. We also found a significant interaction effect of transition and ethnicity with regard to ARE. In immigrant patients, there was less risk reduction after transition than in Dutch patients (HR 0.69 versus 0.10). The overall $P$-value for the model of the effect of transition on graft failure was not significant. We found that only 16% (95% CI 11–24%) of the adolescents with a functioning graft at the time of transition experienced a graft loss in the first 3 years after transition, whereas in the Nottingham study by Watson, this figure was much higher, i.e. 40% (95% CI 22–61%). How can this difference be explained?

In the Nottingham study, this proportion may have been larger than in our study because of the earlier time period in which the study was performed (transition between 1985 and 1997). Recent efforts in the development of a proper transitional care by both paediatric and adult providers alike could have contributed to our improved long-term survival after transition. In the Netherlands, transitional care programs have been developed over time and today regular cooperation between paediatric and adult nephrologists is common practice in all four Dutch centers for paediatric renal transplantation. These days all adolescent patients transfer after thorough preparation, with written as well as oral communication to the adult physician, and there are no unnecessary changes in the drug policy after transition.

Second, Watson primarily focused on the period after transition. In 7 of the 8/20 patients who lost their graft within 3 years after transition, this graft loss was unexpected. However, the additional information on these seven patients showed that, in nearly all of these patients, problems had already started before transition. Four of them had undetectable cyclosporine levels on routine sampling before transition and one patient confessed an episode of non-adherence 6 months prior to transition. Also, five out of these seven patients had been known to have serious adverse psychological problems independent from their

Table 2. Relative risks of acute rejection episodes

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.02 (95% CI 0.97–1.06)</td>
</tr>
<tr>
<td>Male vs female</td>
<td>0.77 (95% CI 0.57–1.03)</td>
</tr>
<tr>
<td>UMCN vs AMC</td>
<td>0.82 (95% CI 0.58–1.16)</td>
</tr>
<tr>
<td>Calendar period (after vs before 1990)</td>
<td>0.93 (95% CI 0.67–1.30)</td>
</tr>
<tr>
<td>Living related donor vs cadaver</td>
<td>0.43 (95% CI 0.24–0.75)</td>
</tr>
</tbody>
</table>

Interaction effects

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>After vs before transition Dutch</td>
<td>0.10 (95% CI 0.04–0.28)</td>
</tr>
<tr>
<td>After vs before transition immigrant</td>
<td>0.69 (95% CI 0.33–1.43)</td>
</tr>
<tr>
<td>Immigrant vs Dutch before transition</td>
<td>1.24 (95% CI 0.84–1.82)</td>
</tr>
<tr>
<td>Immigrant vs Dutch after transition</td>
<td>8.18 (95% CI 2.84–23.60)</td>
</tr>
</tbody>
</table>

Clues for non-adherence. There were 195 ARE as noted before. In all the medical charts, there were only 25 notes describing suspicion of non-adherence at the time of an ARE by the treating physician. Recent medication trough levels in the patient’s blood preceding an ARE showed 24/94 levels <100 μg/L and 4/94 <50 μg/L for cyclosporine and 4/14 levels <4 μg/L for tacrolimus.

Cox proportional hazard model

Transition and the risk of ARE. We analysed the effect of transition on ARE as end point of interest. The model showed an overall effect of transition, which was highly significant ($P < 0.0001$). There was no significant interaction effect when comparing the effect of transition by gender ($P = 0.62$) and by centre ($P = 0.23$). However, there was a significant interaction effect between transition and ethnicity ($P = 0.004$). Table 2 shows the results from the Cox model. The hazard ratios (HR) of age (at the time of an ARE), gender, centre, calendar period (i.e. before or after 1990) and donor source were not significant. The HR of ARE for immigrant versus Dutch patients did not differ significantly before transition. After transition, compared to before transition, the Dutch patients had a significantly lower risk of ARE with an HR of 0.10 [95% confidence interval (95% CI) 0.04–0.28]. In immigrant patients, this risk reduction was not statistically significant with a HR of 0.69 (95% CI 0.33–1.40).

Transition and risk of chronic rejection. Further, we analysed the effect of transition on chronic rejection as end point of interest. The model showed a non-significant overall effect of transition ($P = 0.06$). There was a significant interaction effect between ethnicity and transition ($P = 0.01$). The HR for chronic rejection in Dutch patients after transition compared with before transition was 0.14 (95% CI 0.037–0.52). For the immigrant patients, the HR was 2.8 (95% CI 0.45–17).

Transition and successive creatinine values. We calculated the slope of the trend line of the successive serum creatinine values per patient as an indication for the GFR of the renal allograft using a random effects model. We analysed these slopes by comparing the trend line of all patients before transition with the trend line of the patients after transition. We found no significant difference in the estimate of the graft function before and after transition ($P = 0.193$).
into account the current guidelines, the timing of transition should be influenced by various personal and clinical circumstances. According to Shemesh et al. [9], the majority of adolescent transplant recipients remain adherent to the medical regime. This suggests that having a chronic disease may have an influence on normal adolescent development, but further research is needed to understand the factors that contribute to non-adherence in this population.

Another difference may be due to the selection of patients for transplantation. In our centre, we do not enlist patients on the transplantation waiting list who show non-adherence behavior during chronic dialysis. We know from oral communication that most centres follow the same policy. So, at least in the Netherlands, there is a positive selection in adolescent renal transplantation towards the more adherent patients.

The most important limitation of this study is its retrospective nature, which prohibits accurate insight in the clinical decision-making. The moment of transition for instance is not fixed at a certain age but is generally influenced by various personal and clinical circumstances. According to the current guidelines, the timing of transition should take into account the ‘developmental readiness’, complexity of health problems, characteristics of the adolescent and family and the availability of skilled adult health care providers [11]. Following these guidelines, paediatric nephrologists will tend to keep treating ‘unstable’ and ‘immature’ patients themselves for a longer period than patients who are considered more mature. The median age at transition was 18 years with a wide range, from a minimum of 14 years to a maximum of 22 years. The medical charts showed diverse reasons for transition, e.g. the condition or even failure of the graft, travel distance to the paediatric centre and patient preference. These indicators, and the variation in age at transition, make it difficult to evaluate transition as a single, administrative event. In this study, we have looked at the effect of transition on graft failure. However, it may very well be that the causal relation is the other way around, i.e. the condition of the graft being one of the factors determining the timing of transition to adult care. Four patients lost their graft at the date of transition. The start of dialysis probably was the reason to switch to adult care. The rationale for determining the timing of transition can only be investigated in a prospective study in which this is specifically addressed.

The frequency of ARE in paediatric renal transplant recipients has been assessed in several studies. The rejection rates of the present cohort and the fact that more than half of the subsequent rejections occurred within 1 year after the transplantation are in accordance with the report of a North American study [12]. In comparison with data of adult centres, the rejection rates of children are known to be higher [13]. The suggestion that these higher rates in children may be immunologically driven is in contrast with a study of renal allograft biopsies investigated for immunological markers of rejection in adults and children. No differences were noted [12]. Acute rejection and graft loss have also been linked to age-dependent non-adherence to medical prescriptions [5,14,15]. According to Steinberg, risk-taking behavior is a direct result of an unbalanced development of brain functions involved in affective and motivational regulation on the one hand and cognitive control mechanisms on the other. This sequence of changes favours the development of self-regulation. Prefrontal changes and up-regulation of the dopaminergic system start to take place at around 10 years of age. At the same time, basic cognitive processes, such as working memory and verbal fluency, also develop early in adolescence. However, the maturation of cognitive control mechanisms for higher-order functions, such as future orientation and planning, only takes place from age 16 to the early 20s [20]. Taking this into account, risk behavior is essential for development into independence and non-adherence as a result of normal adolescent development. Thus, in fact it is surprising that the majority of adolescent transplant recipients remain adherent to the medical regime. This suggests that having a chronic disease may have an influence on normal adolescent development as was shown in a Dutch cohort study. Life career milestones to social independence and development were significantly impaired in adolescent renal transplant recipients as compared to the normal population [21].

Contrary to native Dutch patients, immigrant patients remained at risk for ARE over time after transition. There is no reason to believe that the transition policy, access to health care or selection for transplantation has been different in these patients as compared to Dutch patients. Race may influence outcome. African-American children appear to have a significantly increased incidence of ARE. This might be caused by differences in pharmacogenetics [22,23]. Also, differences in the frequency of glomerular disorders may be a contributing factor. They occur more frequently in African-Americans than in Caucasian children and have a poorer outcome compared with structural lesions [24]. However, in our study, the primary diseases in the immigrant group (containing only eight patients of African descent) were comparable to those in the Dutch group. Another possible cause for the apparently worse prognosis in immigrants may be associated with their generally less favourable social and psychological environment, e.g. poor understanding of the language and low social economic status. Thirty years ago, it was already suggested that patients belonging to families whose equilibrium and communication patterns are suboptimal are at risk for non-adherence [25]. It is yet to be investigated which risk factors make adolescent immigrant patients more prone to AREs.

In conclusion, in the adolescent age group, the risk for acute rejection does not increase after transition to the adult unit. The positive effect of transition on ARE may be partly explained by an earlier transfer of relatively stable and adherent patients. This effect was not seen in immigrant patients who had an overall worse outcome. Nephrologists should pay special attention to them. Further prospective research remains necessary to indentify the reasons for the disappointing long-term allograft survival in adolescent renal recipients, especially in immigrants.

Conflict of interest statement. None declared.
Sirolimus and microcytosis

References


Anaemia, microcytosis and sirolimus—is iron the missing link?

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Abstract

Background. Sirolimus (SRL) has been implicated in the causation of post-transplantation anaemia (PTA). It also induces profound red blood cell (RBC) microcytosis, which is poorly understood.

Methods. We conducted a retrospective study of SRL-induced anaemia and microcytosis [mean corpuscular volume (MCV) <80 fl] with specific reference to iron homeostasis in 93 renal transplant patients treated with SRL for at least 3 months.


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