Study of intercurrent infection pattern in hepatitis C seropositive renal transplant recipients, relationship with T-cell function

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ABSTRACT

Background: We assessed the effect of hepatitis C seropositivity on the percentage of various T-cells in living donor renal transplant recipients (LDRTRs) and their association with intercurrent infections post renal transplantation (post-Tx).

Methods: One hundred and thirty-three matching LDRTRs [A (seronegative) (68 patients) and B (seropositive) (65 patients) by ELISA] were studied prospectively 10 days, 6 months and 12 months post-Tx for intercurrent infections, acute rejection and T-cell% by flow cytometry.

Results: CD4⁺, CD8⁺, CD4/CD8 were significantly higher 10 days post-Tx in Group B compared to Group A, \( p < 0.001 \). A significant increase in CD8% was seen 6-month post-Tx among Group B compared to Group A. No difference was detected between groups in (CD4⁺, CD8⁺, CD4/CD8, CD3–CD16/65⁺%), rate and severity of intercurrent infection, rate of acute rejection, 12 months post-Tx. A significantly higher rate of severe infections particularly urinary tract infections (UTI) was noted in Group B compared to Group A the first 3 months post-Tx particularly in those who received the combination of antithymocyte globulin (ATG) or basiliximab, tacrolimus, steroids, mycophenolate mofetil (MMF). CD4⁺% correlated negatively with intercurrent infections in Group B 6 months post-Tx.

Conclusion: HCV⁺ patients are more prone to intercurrent infections the first 3 months post-Tx. Infection rate correlates positively with pre-transplant HCV seropositivity and immunosuppressive regimen.

Introduction

Infection is a major cause of morbidity and mortality in kidney transplant recipients. However, because transplant recipients may not manifest typical signs and symptoms of infection, diagnoses may be confounded.

Infections related to transplant surgical complications, acquisition of health care-associated pathogens, and reactivation of latent disease can affect graft function and transplant outcome.

Hepatitis C virus (HCV) infection is quite common among renal transplant recipients (RTRs), so as intercurrent infection. The incidence of infection following renal transplantation (RTx) varies due to numerous factors particularly, the degree of immunosuppression, the need for anti-rejection therapy and the occurrence of surgical complications.

The behavior of hepatitis C in a state of immunodeficiency is poorly understood. Although, great wealth of data exists that HCV addresses the issue of survival in HCV-infected RT recipients, the critical question of how HCV infection alters the immune status post-Tx as well as the rate of intercurrent infection still remains unanswered. A diligent search of literature did not reveal any comprehensive study addressing this issue. Thus, this study was carried out to study the possible relationship between HCV seropositivity and pattern of intercurrent infection, and host immune response parameters, that is, certain T-lymphocytes subsets (T-helper and T-suppressor) as well as natural killer (NK) cells 6 months post-transplantation among LDRTRs.

Subjects and methods

Patients of this prospective, observational study were recruited from the Transplant Units of two tertiary care hospitals located in Cairo, Egypt. One hundred and thirty-three LDRTRs underwent RTx between July 2013 and October 2014. Collected information included patient demographics, underlying disease, dialysis modality or previous renal transplant, induction and maintenance immunosuppressive regimens, donor
characteristics and detailed information on each infectious episode.

Sixty-eight HCV seronegative (Group A) and 65 HCV seropositive (Group B) LDLTRs as tested by ELISA (third generation) were monitored for infectious episodes for 12 months post-Tx.

The studied groups were negative for hepatitis B virus (HBV) and HIV infection. Smokers, diabetics, patients with advanced liver disease (child classification Classes B and C), patients with chronic infectious diseases, and malignancy were excluded from the study. None of our patients was given antiviral treatment. The study protocol was approved by the ethical committee of institutes from which patients were recruited, and informed consent was obtained from all participants before inclusion in the study.

Methods

All studied subjects were subjected to: full history and clinical examination, assessment for infectious episodes (type, time, severity, relation to graft rejection, etc.), relevant laboratory parameters and phenotypic characterization of T-cell subsets and NK cells%: CD16, CD56, CD4, CD8 and CD4/CD8 which was performed by flow cytometric immunophenotyping 10 days, 6 months and 12 months post-Tx (Coulter® Epics XL-MCLTM Flow Cytometer from Beckman Coulter, Brea, CA).

Definitions

An infectious episode was defined as a confirmed infection requiring hospital admission or every febrile episode with a clinic laboratory diagnosis of infection. The site of infection was determined as urinary, intra-abdominal, vascular catheter-related, pulmonary, soft tissue, primary bloodstream or unknown, according to Centers for Disease Control and Prevention definitions.5

Statistical analysis

Data obtained from the present study were computed using the Statistical Package for the Social Sciences version 17 (SPSS Inc., Chicago, IL) under the platform of Microsoft Windows XP, Professional Edition. Continuous data were expressed in the form of mean ± standard deviation (SD) or range and median while categorical data were expressed in the form of count and percentage. Comparison of quantitative data was done using Student’s t-test or one-way analysis of variance with least significant difference post hoc test for independent samples. Comparisons of continuous data were performed utilizing Mann–Whitney U-test or Kruskal–Wallis test, while categorical data were done using chi-squared test. To measure odds ratios of categorical data and their significance, we used the crosstabs method with risk estimation. Multivariate analysis was used to assess the correlation between phenotypic markers and risk of intercurrent infection post-Tx.

p-Values <0.05 was considered statistically significant.

Results

Patient characteristics

One hundred and thirty-three patients (133) of overall mean age of 45 ± 13 years (median = 46; range = 12–76), underwent Rtx during the study period. All grafts were obtained from living donors (related in 63 and from a non-related donor in 70 cases). Before Rtx, all patients had been on hemodialysis. Eight patients of Group B and 10 of Group A had previously undergone an Rtx and therefore had been excluded from the study. The main causes of renal failure were hypertension (n = 63; 47.2%), vasculitis (n = 13; 9.8%), chronic glomerulonephritis (n = 11; 8.3%), focal segmental glomerulosclerosis (n = 11; 8.3%), polycystic kidney disease (n = 8; 6%), reflex nephropathy (n = 8; 6%), tubulointerstitial nephritis (n = 5; 3.8%), whereas the underlying disease was not identified among the remaining patients (n = 14; 10.6%). One hundred and four recipients (78%) were CMV seropositive and 27 (20%) seronegative. Regarding donors, 100 (75%) were CMV positive and 31 (23%) CMV negative.

Group A and B had similar demographic and clinical data (Table 1). As regard the biochemical parameters, Group B had lower serum albumin, p < 0.001, than Group A. Group B had a higher AST level (median 28.5) versus Group A (median 18), p < 0.001. ALT was significantly higher in Group B compared to Group A (median 29.5 versus 24), p < 0.05 (Table 1).

On Day 10 post-transplantation (post-Tx), CD4% (59.1 ± 370 vs. 35.8 ± 9.5%, p < 0.001), CD8% (59.8 ± 32 vs. 34.0 ± 9.5%, p < 0.001) lymphocytes and CD4/CD8 (1.57 ± 0.4 vs. 1.22 ± 0.5%, p < 0.001) were significantly higher in Group B compared to Group A. Six months post-Tx, CD8% was significantly higher among Group B compared to Group A (58.6 ± 1.4 vs. 32.000 ± 9; p < 0.006). During the late post-Tx period (12 months post-Tx), cellular phenotypic markers were similar in both groups (Table 2).

During the study period, 80 infectious episodes occurred in 70 patients: 45 (64%) had one, 20: two, 2: three, 1: four and another one: five infectious episodes. The most common infections are shown in Table 3.
One third of urinary tract infections (UTIs) were associated with bacteremia. (44/80; 55%) of all infective episodes occurred during the first 3 months post-Tx and 23 (29%) between 3 and 6 months. The mean duration of hospital stay for each infectious episode was 13.22 ± 14.06 days (median = 12.5; range = 1–110).

Group B were more frequently exposed to infections requiring hospital admission (mostly UTI), p = 0.035, 0–3 months post-Tx. Furthermore, the frequency of infection episodes was higher in Group B compared to Group A (mostly respiratory) (borderline significance, p = 0.062) 3–6 months post-Tx (Table 4) (Figure 1).

In the regression analysis, the association of individual immunologic variables with the risk of intercurrent infection in Group B patients was examined. On Day 10 post-Tx, no correlation was found between phenotypic markers and rate and severity of intercurrent infection. During late post-Tx period, that is 6-month post-Tx, a significant inverse correlation existed between CD4 and infection episodes in Group B (HCV+)(p = 0.031) (Figure 2).

There was a positive significant correlation between blood urea, serum creatinine and the prevalence of infections requiring hospital admission (correlation coefficient 0.179, p = 0.020; correlation coefficient 0.265, p = 0.000, respectively) in Group B. A positive significant correlation between blood urea and infections treated in OPC (correlation coefficient 0.155, p = 0.043) existed as well in Group A (HCV−).

**Risk factors**

To identify possible prognostic or risk factors, we compared the characteristics of the 70 patients with infections with the 63 patients without infections (Table 5). Among the significant risk factors for infections during the first year post-Tx were pre-transplant HCV

Table 1. Demographic and clinical characteristics of studied groups.

| Characteristic                  | A              | B              | p-Value |
|-------------------------------|----------------|----------------|---------|
| Age (years)                   | 32.35 ± 7.7    | 37.25 ± 8.2    | 0.077   |
| Sex: male/female (n)          | 48 (70%)/20 (30%) | 45 (70%)/20 (30%) | 0.7     |
| BMI (kg/m²)                   | 25.6 ± 5.5     | 24.6 ± 4.3     | 0.38    |
| Duration of dialysis before Tx (months) | 7.322.80     | 13.839.86     | 0.003   |
| Pre-Tx cross match            | All negative   | All negative   | NS      |
| HLA typing                    | Complete match-29 Haplomatch-23 | Haplomatch-44 1Ag-match-16 | NS |
| Primary diagnosis             | HTN/CGN/APKD/FSGS/reflux nephropathy/ IgAnephropathy/vasculitis/others | HTN/CGN/APKD/FSGS/reflux nephropathy/ IgAnephropathy/vasculitis/others | 8.077 ± 0.97 |
| Serum viral load pre-Tx (log10 copies/mL) | NS           | NS            |
| HCV genotype                  | Genotype 4     | NS            |
| Maintenance immunosuppressive regimen | NS           | NS            |
| Cyclosporine/MMF/prednisolone | (52) 39%       | (39) 29%       | <0.001* |
| Tacrolimus/MMF/prednisolone   | (23) 17%       | (19) 14%       | <0.001* |
| Minimum follow-up             | 12 m           | 12 m           | NS      |
| Biochemical parameters        |                |                |
| Hb (g/dL)                     | 11.080 ± 2.5262 | 11.380 ± 2.0915 | 0.316   |
| Albumin (g/dL)                | 3.730 ± 0.3541 | 3.665 ± 0.3924 | <0.001* |
| SGOT (AST), IU/L              | Median = 18, range = 6–26 | Median = 28.5, range = 12–64 | <0.001* |
| SGPT (ALT), IU/L              | Median = 24, range = 13–37 | Median = 29.5, range = 16–81 | <0.001* |
| Alkaline phosphatase, IU/L    | 72.67 ± 18     | 76.36 ± 123.3 | NS      |

NS: not significant. *Significant.

Table 2. Phenotypic markers in groups a (HCV−) and B (HCV+) 10 days, 6 and 12 months post-tx.

| T cell (%) | A        | B        | p-Value | A        | B        | p-Value | A        | B        | p-Value |
|------------|----------|----------|---------|----------|----------|---------|----------|----------|---------|
| CD4+       | 35.8 ± 9 | 59.1 ± 37| 0.001*  | 56.2 ± 4 | 37.3 ± 12| NS      | 42.2 ± 9 | 31.2 ± 1 | NS      |
| CD8+       | 34.0 ± 9 | 59.8 ± 32| 0.001*  | 32.0 ± 9 | 58.6 ± 1 | 0.006*  | 38.6 ± 24| 49.0 ± 1 | NS      |
| CD4/CD8    | 1.22 ± 0 | 1.57 ± 0  | 0.001*  | 1.47 ± 8 | 1.15 ± 3 | NS      | 1.10 ± 2 | 0.63 ± 6 | NS      |
| CD3-CD16/56| 18.5 ± 12| 17.3 ± 129| NS      | 12.59 ± 79| 13.160 ± 2| NS      | 5.14 ± 3.5 | 5.99 ± 4 | NS      |

Values represented as mean ± SD. *Significant.

Table 3. Infective agents in different time periods after RTx.

| Causative agent          | 0–3 months | 3–6 months | 6–12 months | Total, n (%) |
|--------------------------|------------|------------|-------------|--------------|
| Bacteria                 | 46         | 12         | 8           | 66 (82.5)    |
| E. coli                  | 20         | 4          | 4           | 28 (35.3)    |
| Klebsiella pneumonia     | 9          | 2          | 2           | 13 (16.2)    |
| Pseudomonas aeruginosa   | 7          | 0          | 1           | 8 (10)       |
| Enterococci              | 31         | 4          | 0           | 35 (43.8)    |
| Staphylococcus aureus    | 1          | 1          | 0           | 2 (2.5)      |
| Other                    | 6          | 2          | 1           | 9 (11.2)     |
| Viruses                  | 0          | 3          | 5           | 8 (10)       |
| CMV                      | 0          | 3          | 5           | 8 (10)       |
| Fungi                    | 0          | 2          | 2           | 4 (5)        |
| Candida albicans         | 0          | 2          | 2           | 4 (5)        |
| Unknown                  | 0          | 0          | 3           | 3 (3.8)      |

One third of urinary tract infections (UTIs) were associated with bacteremia. (44/80; 55%) of all infective episodes occurred during the first 3 months post-Tx and 23 (29%) between 3 and 6 months. The mean duration of hospital stay for each infectious episode was 13.22 ± 14.06 days (median = 12.5; range = 1–110).

Group B were more frequently exposed to infections requiring hospital admission (mostly UTI), p = 0.035, 0–3 months post-Tx. Furthermore, the frequency of infection episodes was higher in Group B compared to Group A (mostly respiratory) (borderline significance, p = 0.062) 3–6 months post-Tx (Table 4) (Figure 1).
seropositivity (OR = 3.053; 95% CI = 1.007–9.349; \( p = 0.043 \)) and immunosuppressive protocol including tacrolimus–mycophenolate mofetil (MMF)–steroids with ATG/basiliximab (OR = 3.8824; 95% CI = 1.1821–12.7507; \( p = 0.025 \)).

There was an increased prevalence of CMV infection after the completion of valganciclovir prophylaxis (OR = 20.7260; 95% CI = 1.1569–371.2953; \( p = 0.0395 \)).

The number of acute rejection episodes was similar in both groups (Table 5).

Four out of 70 patients (5%) with infection episodes had fatal outcomes.

**Discussion**

In the HCV\(^+\) RTRs, in a milieu of immunosuppression, the patient’s response to intercurrent infection post-Tx has not been adequately studied. The progression of liver disease post-Tx and the patient’s reaction to acquired intercurrent infection post-Tx depends on the balance between host immune response to the virus, the ability of the virus to modulate the host immune response for its survival and the type of immunosuppressive therapy post-Tx.\(^3\)

The major findings of our study were the following:

(i) Group B patients on Day 10 post-Tx showed significantly higher percentages of CD4\(^+\), CD8\(^+\), CD4/CD8 compared to Group A and a significantly increased CD8\(^+\) was seen 6 months post-Tx among Group B patients compared to Group A. No difference was detected between groups in cellular phenotypic markers (CD4\(^+\), CD8\(^+\), CD4/CD8, CD3–CD16/65\(^+\)), rate of acute rejection, nor patients survival 12 months post-Tx (Table 2).

(ii) The number of acquired intercurrent infections was similar in Group A and B 12 months post-Tx (Table 4). The overall frequency of infection episodes was
higher in Group B (HCV\(^+\)) compared to Group A (HCV\(^-\)) particularly UTI and the difference was particularly significant 0–3 months post-Tx, \(p = 0.035\) (Table 4). (iii) There was a significant negative correlation between CD4% and infection rate in Group B (HCV\(^+\)) (\(p = 0.031\)) 6 months post-Tx.

In this study, Group A and B had similar demographic and clinical data (Table 1). As regard the biochemical parameters, Group B had lower serum albumin, \(p < 0.001\) compared to Group A. Group B had a higher AST level (median = 28.5) versus A (median = 18), \(p < 0.001\). ALT was significantly higher in Group B compared to Group A (median = 29.5 versus 24), \(p < 0.05\) (Table 1). Abnormal liver biochemistry is uncommon following renal transplant in individuals with HCV who had normal liver biochemistry preceding transplantation.\(^6\) The significantly higher liver enzymes and lower serum albumin in Group B compared to Group A could be due to increased activity of liver disease by the immunosuppressive therapy post-transplant. There are data to support the fact that HCV RNA levels do rise with high doses of steroids, although they fall back to normal once therapy is reduced.\(^7\) Another explanation is the fact that this could be attributed to more advanced liver disease in that population despite normal liver enzymes pre-transplant. Pre-transplant assessment of HCV\(^+\) renal transplant candidates should likely include a liver biopsy as serum transaminase levels and HCV RNA are a poor reflection of the degree of underlying chronic hepatitis C.\(^6\)

The cellular phenotypic markers studied are demonstrated in Table 2. On Day 10 post-Tx, the percentage of CD4, CD8 and CD4/CD8 among Group B patients were significantly high in comparison with Group A. During the late post-Tx period (6 months post-Tx), a significant increase in the percentage of CD8 T-cells was observed.
Patterns of intercurrent infection in both groups of our studied population are also illustrated in Table 4. The total number of infection episodes in both Groups (A and B) first year post-Tx mainly consisted of UTI (38.5%), pneumonia (23.5%), surgical wound infections (5%), intra-abdominal (20%), intravascular line (4%), primary bacteremia (5%) and others (4%). Similar types of infection were found post-Tx by Karuthu and Blumberg, 2012.2 UTI was the most common infection first 3 months post-Tx. This observation agrees with data from USA and Holland where 40–60% of infections occurred in the urinary tract.11,13 In our study, the most common bacterial cause of UTI was Escherichia coli (E. coli) in half of the cases, similar to the prevalence in the Dutch study.13 In the study from the United States, the commonest cause was Enterococcus spp. (one third of cases) and E. coli, the second commonest (one-fifth), presumably reflecting geographic differences in the prevalence of uropathogenic organisms.14

The prevalences of lower respiratory tract and CMV infections were similar to other reports.11 The eight cases of hospitalization owing to CMV infections were all observed after the end of the 3-month chemoprophylaxis period, as reported elsewhere.16

Despite the proven effectiveness of prophylaxis of bacterial and CMV infections, it seems that the first 3 months after transplantation remain the most dangerous concerning infectious episodes.17

Post-transplant infections may follow a predictable pattern with regard to timing after transplant.15 In the current study, early infections (within the first month) were more likely due to nosocomially acquired pathogens, surgical issues, and some donor-derived infections. Opportunistic pathogens occurred later, during the subsequent 5 months, reflecting the greater impact of immunosuppressive therapies. Late post-transplant, infections occurring during that period were mainly secondary to opportunistic pathogens or conventional ones; opportunistic pathogens were more frequently seen in patients who required greater immunosuppression or who had specific environmental exposures. Fishman16 (2007) have noted that although a time line of infections might be helpful, the pattern and timing of infections may be significantly altered by the choice of immunosuppressive agents that may affect the net state of immunosuppression at different time points, as well as the choice and duration of antimicrobial prophylactic agents.

Among the significant risk factors for infections during the first year post-Tx were pre-transplant HCV seropositivity and immunosuppressive protocol including tacrolimus–MMF–steroids with ATG/basiliximab. This observation suggests that qualitative and quantitative

(which may confer protective immunity) whereas activated helper T-lymphocytes were reduced among HCV-positive RTRs compared with Group A.

Similar findings were reported by Snyder et al.8 (2009). These findings are also in agreement with Justa et al. who studied Cellular Immune Response and Cytokine Profile Among Hepatitis C positive and negative Living Donor Renal Transplant Recipients in 50 patients where they found on Day 10 post-Tx, a significant increase in the counts of CD4, CD8 lymphocytes and CD4/CD8 and NK cells among HCV+ patients in comparison with a seronegative group, a significant increase in the number of CD8 T-cells among HCV-positive RTRs compared to seronegative ones and no significant difference in the mean number of helper/inducer T-cells, and NK cells between HCV+ and HCV− patients 6 months post-Tx.9 Similar findings were reported by Alamartine et al.10 (1992). Several authors11–15 have also previously shown that cytotoxic T-lymphocytes were increased in number, whereas activated helper T-lymphocytes and NK cells were reduced in renal allograft recipients with HCV infection in comparison with controls.

A reduced CD4/CD8 ratio has been reported in long-term renal allograft recipients.12 That the slightly reduced ratio in our study didn’t reach statistical significance may be attributable to shorter post-Tx duration, or the different immunosuppressive therapy in our study.

In the present study, we have also described the characteristics of infections among RTRs in the first year post-Tx. Nearly half of our patients were admitted for an infectious episode during that time period. In a Dutch study in 2001, 71% of recipients were admitted with an episode during the first year post-Tx, a rate significantly higher than ours.13

Fifty-five percent of the infectious episodes happened during the first 3 months, an alarming prevalence comparable to that described in the literature. The United States Renal Data System has reported admission rates owing to infections during the first year post-transplant to rise from 32 to 38% between 1994 and 2004. This incidence was lower than that in our study, possibly owing to variable criteria for patient admission and the presence of day care units in many USA centers that have contributed to reduced hospital in-patient admissions.14,15 These variables reflect the difficulty in comparing infection prevalences among centers and countries.

The frequency of infection episodes was higher in Group B compared to Group A and the difference was statistically significant, p = 0.035 first 3 months post-Tx (Table 4).
modifications of prophylaxis schemes may be useful in these patients.

In agreement, several early studies found a significantly increased risk for infections in HCV-infected recipients,\textsuperscript{7,17–19} with the highest risk in the first 6–12 months after transplantation.\textsuperscript{7,18} Contrary to these earlier studies as well as to ours, no significant differences in infection rates between HCV-infected and HCV-negative recipients were reported in a meta-analysis by Fabrizi et al.\textsuperscript{20} A multicenter study also showed no difference in overall incidence of infections (bacterial, viral and fungal) between the two groups, with HCV being an independent factor only for bloodstream infections.\textsuperscript{21} Interestingly, in a single retrospective case-control study, HCV infection was found to be an independent risk factor for tuberculosis post-Tx.\textsuperscript{22}

Similarly, Kosmadakis et al.\textsuperscript{23} (2013) reviewed the effects of immunosuppressive regimens, the regimen including tacrolimus–sirolimus/everolimus–methylprednisolone–daclizumab was associated with significantly higher infection rates. The patients who received this intensive immunosuppressive regimen usually were characterized as high immunologic risk, namely, a high percentage of cytotoxic antibodies and/or positive B-flow cross-match.

Because of numerous potential glucocorticoid (GC) toxicities and calcineurin inhibitors (CNI) toxicities, many new regimens have been developed that incorporate rapid GC elimination, or CNI dose reduction or elimination.\textsuperscript{24,25} Rapid GC withdrawal within the first few days after transplantation is usually achieved with antibody induction.\textsuperscript{21} The effect of different immunosuppressive agents on the outcome in HCV-infected RTRs has been reviewed\textsuperscript{3} and further prospective studies are needed before definite recommendations regarding the choice of immunosuppressive regimens in these patients can be made. HCV per se, did not have any significant effect on graft or patient outcome in this case-control study one year post-Tx. In this study, the immunosuppressive regimen was similar between Group A and B, and so was the number of acute rejection episodes (Table 5).

Many studies have reported no difference in the number of rejection episodes and graft loss between HCV-infected and non-infected renal allograft recipients.\textsuperscript{23,24}

There was a significant negative correlation between CD4 and infection rate in Group B (HCV\textsuperscript{–}) ($p = 0.031$). Calarota et al.\textsuperscript{26} regularly assessed the CD4\textsuperscript{+} and CD8\textsuperscript{+} T-cell numbers during the first 8 months after kidney and heart transplantation and reported that those patients who developed opportunistic infections had lower counts as compared with those without. Various authors as well have consistently shown that the risk of various intercurrent infections after kidney transplantation is increased in recipients with low CD4\textsuperscript{+} T-cell counts.\textsuperscript{27–31} Like noted in the current study, Chan et al.\textsuperscript{11} as well have previously showed that activated helper T-lymphocytes and NK cells were reduced in renal allograft recipients with HCV infection 6 months post-Tx in comparison with controls. In the current study, the observed reduction of activated helper T-cells (CD4) and NK cells in HCV\textsuperscript{+} patients may depict mechanisms contributing towards viral persistence. Similar observations were reported by other authors\textsuperscript{12,13} but in patients with chronic HBV infection.

Chan et al.\textsuperscript{11} have also previously showed that cytotoxic T-lymphocytes were increased in number, whereas activated helper T-lymphocytes and NK cells were reduced in renal allograft recipients with HCV infection in comparison with control patients. This is also in agreement with Manuel et al.\textsuperscript{24} (2012) who studied the activation of NK cells during microbial infections. The authors have demonstrated a strong body of evidence to implicate NK cells in effective control of a diverse array of pathogens, including viruses, bacteria, protozoa, helminths and fungi.

Whilst many of these infections can be contained in the absence of NK cells, clearance of these organisms is almost always more efficient and more complete in the presence of a functional NK cell response. NK cell activation by pathogens occurs predominantly via the indirect pathway involving cytokines and cell contact dependent signals from accessory cells.\textsuperscript{22}

It may be concluded that hepatitis C seropositive LDRTRs are at increased risk of intercurrent infection compared to seronegative ones and this risk is more apparent in long term follow up and that attention to this increased risk, including adjustment of duration of chemoprophylaxis against particular pathogens as well as adjustment of anti-rejection regimen may be needed in such candidates.

**Disclosure statement**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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