Clinical Study

Renal Transplantation in Hepatitis C Positive Patients: A Single Centre Experience

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1. Introduction

Hepatitis C virus (HCV) infection is an independent risk factor for renal transplantation (RTx). Immunosuppression minimization can render better quality of life to these patients. Methods. We analyzed 132 HCV-positive RTx patients (group A) transplanted under tolerance induction protocol (TIP) and compared them with 79 controls (group B) transplanted using standard triple drugs. TIP consisted of 1 donor-specific transfusion, peripheral blood stem cell infusion, portal infusion of bone marrow, and target-specific irradiation. Their immunosuppression was cyclosporin, 2 ± 1 mg/kgBW/day + prednisone, 10 mg/day. Results. TIP had no side effects. Although unequal in size, the groups were well balanced. Group A patient survival at 1, 5, and 10 years was 92.4%, 70.4%, and 63.7%, respectively, versus 75.6%, 71.7%, and 55.7% in later, and graft survival was 92.9%, 81.5%, and 79.1% versus 91.7%, 75.7%, and 67.7%, respectively. Mean serum creatinine (mg/dL) at these time periods in former was 1.38, 1.72, and 1.87, versus 1.3, 1.75, and 2.1 in later. Altered liver functions were noted in 22% patients in former versus 31% in later. Group A had lesser rejection episodes. Conclusion. RTx using TIP in HCV-positive patients is a viable option with acceptable outcome.
2.1. HLA Typing and LCM. HLA typing and LCM were done by conventional serological technique (one lambda predot trays were used for HLA A, B, and DR typing). LCM was done by serological method using auto dithiothreitol and standard cytotoxicity methods with T and B lymphocytes each.

2.2. Patient Demographics. Of 211 patients studied, group A comprised of 132 patients who were transplanted under TIP with low-dose immunosuppression. Group B consisted of 79 patients, considered as controls who opted out of protocol. Demographics of both groups were fairly balanced (Table 1). Mean patient age of group A was 35.1 years with 92.4% males and in group B was 34.2 years, with 74.6% males. Mean donor age was 43.2 years in the former and 40.6 years in the latter.

Table 1: Demographics of renal transplant HCV-positive patients (group A) and control patients (group B).

| Patients (n = 211) | Group A (n = 132) | Group B (n = 79) |
|-------------------|-------------------|-----------------|
| Mean age (years; ± SD) | 35.1 ± 11.2 | 34.2 ± 11.4 |
| Mean donor age (years; ± SD) | 43.2 ± 11.1 | 40.6 ± 11.4 |
| Patient gender (male : female) | 122 : 10 | 59 : 20 |
| Third-party infusions | 13 ± 3 | 12 ± 3 |
| HLA match: n/6—in percentage | | |
| 0 | 12.1 (n = 16) | 5.1 (n = 4) |
| 1 | 18.9 (n = 25) | 7.6 (n = 6) |
| 2 | 25.8 (n = 34) | 10.1 (n = 8) |
| 3 | 30.3 (n = 40) | 34.1 (n = 27) |
| 4 | 5.3 (n = 7) | 8.9 (n = 7) |
| 5 | 1.5 (n = 2) | 3.8 (n = 3) |
| 6 | 0 | 0 |
| Not performed | 6.1 (n = 8) | 30.4 (n = 24) |

Basic disease—in percentage

| Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; CGN: chronic glomerulonephritis; CTIN: chronic tubulointerstitial nephritis; DM-DN: diabetes mellitus, diabetic nephropathy; FSGS: focal segmental glomerulosclerosis; HUS: hemolytic uremic syndrome; MMF: mycophenolate moftetil; MN: membranous nephropathy. |

No immunological preconditioning of the recipient was done. Graft-versus-host disease (GvHD) was ruled out by monitoring absence of skin rashes, gastrointestinal symptoms, abnormal liver function tests, and evidence of BM suppression.
years in later. Donors were mainly parents, spouses/siblings in both groups with mean HLA match 3 ± 1.2 in former and 3 ± 1.1 in later. The commonest etiology of CRF was chronic glomerulonephritis (CGN) in both groups, with 50% patients in former and 34.2% having CGN in the later. Mean third party infusions were 13 ± 3 in former and 12 ± 3 in the later.

2.3. Recipient Immunosuppression

**Group A.** CsA was the principal immunosuppressant with prednisolone, 10 mg/day. CsA doses were adjusted with an intention to maintain trough blood levels of 50–176 ng/mL (EMIT 2000 CsA assay, USA). Mean trough levels of CsA were 180 ± 20 ng/mL in 1st 2 months of transplantation and tapered to maintain 100 ± 15 ng/mL thereafter.

**Group B.** In addition to the above drugs, group B received mycophenolate mofetil (enteric coated), 360 mg twice a day/Azathioprine, 1.5 mg/kg BW/day and doses adjusted according to BM function.

2.4. Rejection and Its Treatment in Both Groups. Protocol biopsies were performed at 100 days of stable graft function in subset of patients. Rejection was diagnosed on biopsy, reported as per modified Banff criteria, and treated accordingly [4, 5]. Rejections were treated with intravenous methylprednisolone, 250 mg/day × 3. Resistant rejections were treated by CsA replacement with tacrolimus in both groups. MMF/azoran was added in group A.

They were also covered with prophylaxis for CMV and pneumocystis carinii. Efficacy of protocol was tested by comparing patient and graft survival, incidence of rejections, HCV reactivation, quality of graft function, and immunosuppression requirement.

2.5. Statistical Analysis. Students’ paired t-test was carried out to compare the graft function in terms of SCr, rejection episodes, and survival analysis. Survivals were examined using Kaplan-Meier analysis and compared using the log-rank test.

3. Results

Side effects of G-CSF in donors were malaise, mild pyrexia, and occasional skin rashes which responded to antipyretic agents. The total average dose of CD34+ cells infused in group A patients was 1.3 ± 1.43 × 10^6 cells/kg BW. Out of 132, 18 (13.6%) patients became positive on 12th day of TIP, out of them, 11 patients became negative after waiting for 8–10 days and 7 patients underwent 2 plasmapheresis and were put on MMF. They were transplanted after they became negative (after 10–15 days).

Regarding transplantation surgery, mean donor data in both groups was similar with mean warm-ischemia time of 25 ± 10 seconds, mean anastomosis time of 30 ± 10 minutes and mean total operation time of 155 ± 20 minutes. Mean followup of group A and B was 8.38 years and 8.95 years, respectively. Mean patient survival in the former at 1, 3, 5, 7, and 10 years was 92.4%, 74.2%, 70.4%, 67.6%, and 63.7%, respectively, as compared to group B with 75.6%, 71.7%, 71.7%, 63%, and 55.7% survival, respectively. Mean graft survival in the former at 1, 3, 5, 7, and 10 years was...
92.9%, 85.6%, 81.5%, 81.5%, 79.1%, respectively, as compared to group B with 91.7%, 81.2%, 75.7%, 67.7%, 67.7%, 92.9%, 85.6%, 81.5%, 81.5%, 79.1%, respectively. Kaplan Meier graphs of patient and graft survival are shown in Figures 2(a) and 2(b).

Graft function in terms of Scr (in mg/dL) in both groups at 1, 3, 5, 7, and 10 years was 1.38 ± 0.29, 1.55 ± 0.34, 1.72 ± 0.47, 1.8 ± 0.39, and 1.87 ± 0.69, versus 1.3 ± 0.37, 1.58 ± 0.64, 1.75 ± 0.61, 1.97 ± 0.73, and 2.1 ± 0.81 in group B. Liver function status was deranged and accompanied by presence of HCV-RNA (tested by PCR and 1 to 5 million copies/mL with mean rate of 1.65 ± 0.75 copies/mL in TIP and 2.3 ± 2.05 copies/mL in controls were noted) in 22% (n = 29) patients of group A out of which 8.3% (n = 11) succumbed to chronic liver failure and in 31% (25 patients) of group B, 16.5% (13 patients) died of chronic liver failure. Group A patients had better graft and patient survival along with graft function status as compared to group B (statistically not significant).

In terms of rejection there was statistically significant decrease in T-cell-mediated rejections and chronic changes in the former as compared to the later (Table 2). Majority of the patients responded to antirejection therapy. However 4/132 (about 3%) in TIP group and 4/79 (about 5%) in control group did not respond and eventually lost their grafts to chronic dysfunction and eventually succumbed to secondary infections and septicemia. Incidence of reactivation of HCV was also significantly less in the former as compared to controls. In TIP group totally 45 (34%) patients and in controls 32 (40.5%) were lost over a followup of 12 years. Out of these 11 in TIP and 13 in controls succumbed to liver failure, others to chronic graft dysfunction-related morbidity or to septicemia. The other advantage in group A was significantly less requirement of maintenance immunosuppression in the form of CsA, 2 ± 1 mg/kg BW and prednisone, 5–10 mg/day versus group B with standard triple drug immunosuppression.

### Table 2: Results.

| Patients (n = 211) | Group A (n = 132) | Group B (n = 79) | P value |
|-------------------|------------------|-----------------|---------|
| Study period      | Jan 99–Dec 06    | Jan 98–Dec 06   |         |
| Mean followup (years; range) | 8.38 ± 2.2 (3.8–11.8) | 8.95 ± 2.2 (4–12.6) |         |
| Mean Scr (mg/dL) at |                  |                 |         |
| 1 year            | 1.38 ± 0.29      | 1.3 ± 0.37      | NS      |
| 3 years           | 1.55 ± 0.34      | 1.58 ± 0.64     | NS      |
| 5 years           | 1.72 ± 0.47      | 1.75 ± 0.61     | NS      |
| 7 years           | 1.8 ± 0.39       | 1.97 ± 0.73     | NS      |
| 10 years          | 1.87 ± 0.69      | 2.1 ± 0.81      | NS      |
| Predominant biopsy findings—percentage | | | |
| Acute rejection episodes—percentage | | | |
| Bcell mediated    | 8.3 (n = 11)     | 15.2 (n = 12)   | NS      |
| Tcell mediated    | 8.3 (n = 11)     | 17.2 (n = 14)   | 0.03    |
| Suspicious T/B    | 9.8/0 (n = 13/0) | 20.2/5 (n = 16/4) | 0.024/0.022 |
| Acute CNI toxicity| 12.1 (n = 16)    | 19 (n = 15)     | NS      |
| Recurrence        | 1.5 (n = 2)      | 2.5 (n = 2)     | NS      |
| Chronic rejections|                  |                 |         |
| Bcell mediated    | 3 (n = 4)        | 6.3 (n = 5)     | NS      |
| Tcell mediated    | 3.8 (n = 5)      | 11.4 (n = 9)    | 0.029   |
| IFTA              | 8.3 (n = 11)     | 19 (n = 15)     | 0.018   |
| Chronic CNI toxicity| 9.1 (n = 12)   | 16.5 (n = 13)   | NS      |
| Recurrence        | 2.3 (n = 3) (ATIN) | 3.8 (n = 2 (ATIN), n = 1 (MPGN)) | NS      |
| De novo nephropathy| 1 (MN)          | 0                | NS      |
| Chronic liver failure due to reactivation | 22 (n = 29) | 31 (n = 25) | P = 0.0002 |

Abbreviations: CNI: calcineurin inhibitor; CGN: chronic glomerulonephritis; CsA: cyclosporin A; ELISA: enzyme linked immunosassay; ESRD: end-stage renal disease; G-CSF: granulocyte colony stimulating factor; HCV: hepatitis C virus; IFTA: unexplained interstitial fibrosis and tubular atrophy; LCM: lymphocyte cross-matching; PBSC: peripheral blood stem cells; POD: postoperative day; RTx: renal transplantation; Scr: serum creatinine; TIP: tolerance induction protocol.

4. Discussion

The effect of pretransplant HCV infection on survival of patients and grafts in RTx is controversial [6]. However, survival is better in HCV RTx patients as compared to dialysis [7]. The goals of pretransplantation HCV therapy are to decrease the risk for progression of HCV-associated liver disease, stabilize renal function in patients with HCV-related glomerulopathy, and prevent development of HCV-associated disease after transplantation [8]. The use of immunosuppression predisposes RTx patients to risks of deranged...
liver functions and mortality [9, 10]. A meta-analysis of natural history of HCV in 6365 RTx patients showed that anti-HCV antibody was an independent risk factor for death and graft failure with relative risk of 1.79 [11]. In our center we offer TIP to all patients, and we start the protocol only after informed consent form is signed by patient, donor, and witness. However, all donors are not willing to undergo stimulation protocols, abdominal fat resection, BM aspiration, and above all they are not willing to wait till renal transplantation. We explain to them that it may take a month or little longer for transplantation, to finish the protocol and if patient becomes lymphocyte cross-match positive, waiting period can become longer. Many patients and donors cannot get leave from their work for such a long period even if they do not have to stay in hospital, they need to visit us frequently which they are not willing. With minimization of immunosuppression, patients are at lower risk of infections and hence return to better quality of life. Secondly lowering of rejection incidence and severity automatically saves financial burden, especially in India where there is no financial support from government medicare/medical insurance. With TIP, use of less number and low-dose of drugs brings down the cost, though we have not touched upon this aspect here. We have more than 10 years of experience of using TIP in about 1500 patients and hence we modified it for HCV-positive patients and implemented it [12]. Our study shows that with use of tolerance induction protocol for HCV-positive patients, quality of life, graft function, and survival are reasonably good even for a long period of ten years. Our control (group B) patients have reasonable quality of graft function and survival as found in other studies [6–11]. Interestingly, tolerance induction protocol yielded significantly less chances of reactivation of HCV as compared to controls. This could be attributed to better immune competence in these patients since they require less immunosuppression.

5. Conclusion

RTx is an acceptable option for HCV-positive patients with ESRD, and tolerance induction protocol is preferable over standard triple drug immunosuppression in this group of patients.

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References

[1] B. J. G. Pereira and A. S. Levey, “Hepatitis C virus infection in dialysis and renal transplantation,” Kidney International, vol. 51, no. 4, pp. 981–999, 1997.
[2] D. Roth, “Hepatitis C virus: the nephrologist’s view,” American Journal of Kidney Diseases, vol. 25, no. 1, pp. 3–16, 1995.
[3] S. M. H. Moghaddam, S. M. Alavian, and N. A. Kermani, “Hepatitis C and renal transplantation: a review on historical aspects and current issues,” Reviews in Medical Virology, vol. 18, no. 6, pp. 375–386, 2008.
[4] L. C. Racusen, R. B. Colvin, K. Solez et al., “Antibody-mediated rejection criteria—an addition to the Banff ‘97 classification of renal allograft rejection,” American Journal of Transplantation, vol. 3, no. 6, pp. 708–714, 2003.
[5] K. Solez, R. B. Colvin, L. C. Racusen et al., “Banff ’05 meeting report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy (‘CAN”),” American Journal of Transplantation, vol. 7, no. 3, pp. 518–526, 2007.
[6] B. Einollahi, B. Hajarizadeh, S. Bakhtiari et al., “Pretransplant hepatitis C virus infection and its effect on the post-transplant course of living renal allograft recipients,” Journal of Gastroenterology and Hepatology, vol. 18, no. 7, pp. 836–840, 2003.
[7] G. A. Knoll, M. R. Tankersley, J. Y. Lee, B. A. Julian, and J. J. Curtis, “The impact of renal transplantation on survival in hepatitis C- positive end-stage renal disease patients,” American Journal of Kidney Diseases, vol. 29, no. 4, pp. 608–614, 1997.
[8] N. A. Terrault and D. B. Adey, “The kidney transplant recipient with hepatitis C infection: pre- and posttransplantation treatment,” Clinical Journal of the American Society of Nephrology, vol. 2, no. 3, pp. 563–575, 2007.
[9] J. M. Morales and J. M. Campistol, “Transplantation in the patient with hepatitis C,” Journal of the American Society of Nephrology, vol. 11, no. 7, pp. 1343–1353, 2000.
[10] F. Fabrizi, P. Martin, and C. Ponticelli, “Hepatitis C virus infection and renal transplantation,” American Journal of Kidney Diseases, vol. 38, no. 5, pp. 919–934, 2001.
[11] F. Fabrizi, P. Martin, V. Dixit, S. Bunnapradist, and G. Dulai, “Hepatitis C virus antibody status and survival after renal transplantation: meta-analysis of observational studies,” American Journal of Transplantation, vol. 5, no. 6, pp. 1452–1461, 2005.
[12] A. V. Vanikar, K. R. Gopalan, A. Feroz et al., “Operational tolerance in living-related renal transplantation: a single-center experience,” Transplantation Proceedings, vol. 43, no. 5, pp. 1551–1558, 2011.