The Effect of Induction Therapy with Basiliximab on the Recurrence of Hepatitis C Virus in Living Donor Liver Transplantation (Retrospective Study)

Wael Safwat[*1] – Rasha Refaie[2] – Medhat Abdel Aal[2] – Ibrahim Mostafa[1] – Mahmoud and El Meteini[3]

[1]Theodor Bilharz Research Institute [2]Wadi Al Neel Hospital 3-Ain Shams University
[*]waelsafwat@yahoo.com

Abstract: Background: Hepatitis C virus (HCV) recurrence in HCV+ liver transplant recipients is almost inevitable and may be promoted by immunosuppression. Basiliximab, a high-affinity chimeric monoclonal antibody functions as an immunosuppressive agent, is effective in reducing acute rejection episodes in liver allograft recipients, but the influence on HCV recurrence might be a problem. **Objectives**: To study the effect of induction therapy with Basiliximab on HCV recurrence in adult living donor liver transplantation. **Methods:** This was a retrospective study to determine the effect of induction therapy with Basiliximab on the recurrence of HCV in the grafted liver. In this study 47 HCV patients were included who passed more than 6 month post-transplantation. All HCV recurrences were all proved histologically. All our patients received corticosteroids in addition to either tacrolimus (FK) or ciclosporine (Neoral), mycophenolate mofetil was given to all except 4 patients. **Results:** From the 47 transplanted patients 14 (29.8%) had HCV recurrence. In the group which used Basiliximab (Group I); the rate of HCV recurrence was 56.3%, while the group in which no Basilximab was used (Group II); the rate of HCV recurrence was 16.1% (P<0.001) highly significant. In patients who had HCV recurrence 64.3% of patients received induction therapy with Basiliximab, meanwhile in the non-recurrent group only 15.2% of patients received Basiliximab (P<0.001) highly significant. To out rule the role of either FK or Neoral in recurrence of HCV, we found that the rate of HCV recurrence was as follows: in a group of patients who received Basiliximab and FK; HCV recurrence occurred in 54.50%, in patients who did not receive Basiliximab but received FK; HCV recurrence occurred in 21.7% (P<0.001) highly significant. In patients who received Basiliximab and Neoral; HCV recurrence occurred in 60% and there was no HCV recurrence in patients who did not receive Basiliximab and received Neoral (P<0.001) highly significant. We also compared two groups of patients; those who received FK and Basiliximab (54.5%) had HCV recurrence, and in those who received Neoral and Basiliximab (60 %) had HCV recurrence (P > 0.05) non significant. **Conclusion:** The rate of HCV recurrence in LDLT is more when Basiliximab was used as induction therapy in patients undergoing LDLT for chronic HCV related end stage liver disease.

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1. Introduction:

Cirrhosis secondary to chronic hepatitis C virus (HCV) infection accounts for most liver transplants performed in transplant centers worldwide (1). Given the high prevalence of HCV infection, the number of patients in need of transplantation will increase. A number of factors may predispose to HCV recurrence (2). Acute graft rejection remains a major problem among additional sequelae in liver transplant recipients. Basiliximab, a chimeric monoclonal antibody with high affinity for the CD25 chain of the interleukin-2 receptor, has significantly reduced the incidence of acute rejection episodes in liver transplant recipients (3) (4). HCV recurrence in post living donor liver transplantation (LDLT) is of utmost importance to prolong both graft and patient survival. Earlier reports stated that LDLT might lead to an increased rates of HCV recurrence due to regeneration of the graft, however with more experience and the increasing number of studies concerning this issue it turned to be the same or even better due to the fact of having a better chance of choosing a better graft with less fat and younger donor age. Multiple factors have been studied as predisposing factors for HCV recurrence; surgical factors as ischemia time and medical factors such as; overweight and steatosis, alcohol intake and immunosuppressive regimens are all incriminated factors. Considering the immunossupression factor, no specific calcineurin inhibitor has been proven up till now superiority over the other in terms of decreased rates of HCV recurrence. The use of corticosteroids and the duration whether long term or rapid tapering or even steroid free protocols gave conflicting results. The use of induction therapy has

not been clearly studied concerning its effect on HCV recurrence in the graft (5).

Objectives:

To study the effect of induction therapy with basiliximab on HCV recurrence in adult living donor liver transplantation.

2. Materials and Methods:

This was a retrospective study. The clinical courses of 47 recipients who were transplanted for HCV end stage liver disease and successfully survived a least 6 months post LDLT were studied. The Immunosuppression regimens for all our patients included corticosteroids which were all tapered within the first 3 months. Calcineurin inhibitors used were either tacrolimus (FK) or ciclosporine (Neoral). Mycophenolate mofetil was given to all except four patients who had monotherapy with tacrolimus as they had hepatocellular carcinoma before transplantation. The diagnosis of Hepatitis C virus recurrence was suspected in cases of elevated liver enzymes with a high level of viraemia with HCV RNA PCR and then all subjected to a liver biopsy and proved histologically by our transplant pathologist. The studied group was divided into two groups; group I had basiliximab as induction therapy included 16 patients and group II had no induction therapy with basiliximab included 31 patients, and the incidence of recurrence was compared between the two groups. **Statistical analysis:** Statistical analyses were performed using SPSS for Windows release 11.0 (SPSS Inc, Chicago, IL, USA).Comparisons were performed between groups of patients (level of $p < 0.05$ were considered significant). Categorical data were analyzed using Pearson's chi-square test, and t-test.

3. Results:

From the 47 patients originally underwent LDLT for HCV ESLD and successfully passed the operation and passed at least 6 months post transplant, Age ranged from 38-62 years, 5 females and 42 males. HCV recurrence occurred in 14 (29.8%) patients. In group I (induction therapy with basiliximab) the incidence of HCV recurrence was 9 (56.3%) patiemts. In group II (no induction therapy with basiliximab) the rate of HCV recurrence was 5 (16.1%) patients ($P<0.001$) which is a highly significant difference between the 2 groups. In the HCV recurrent group 9 (64.3%) patients had induction therapy with basiliximab meanwhile in the non recurrent group only 5 (15.2%) patients had induction therapy ($P<0.001$) highly significant. In order to rule out the effect of the used immunosuppresive drug; either Tacrolimus or neoral on HCV recurrence, the following analysis was done: Rate of HCV recurrence in the group of patients who received basiliximab and FK (11 patients); HCV recurrence occurred in 6 (54.50%) patients, in patients who did not receive basiliximab but received FK (23 patients); HCV recurrence occurred in 5 (21.7%) patients ($P<0.001$) highly significant. In patients who received basiliximab and Neoral (5 patients); HCV recurrence occurred in 3 (60%) patients and there was no HCV recurrence in patients who did not receive basiliximab and received Neoral ($P<0.001$) highly significant. We also compared two groups of patients; those who received FK and basiliximab 11 patients, 6 (54.5%) patients had HCV recurrence, and in those who received Neoral and basiliximab 5 patients, 3 (60 %) patients had HCV recurrence ($P > 0.05$) non significant. All other factors analyzed such as age, sex, biliary strictures had no statistical influence on HCV recurrence in our studied group.

4. Discussion:

Although liver transplantation is the second most common form of solid organ transplantation after renal transplantation, with an increasing rate of LDLT due to organ shortage and HCV being the most common indication for liver transplantation, surprisingly few data are available on the use of immunosuppressive antibody therapy in these patients. The rate of HCV recurrence and the rate of acute rejection episodes post LDLT when compared to cadaveric liver transplantation, is an important question that might influence management strategies. In our study recipients after LDLT, has been evaluated for the effect of induction immunotherapy using basiliximab on the recurrence of HCV. The previous hypothesis that HCV recurrence would be higher in LDLT is debated recently in many studies. However, In a retrospective study of hepatitis C virus (HCV)-infected transplant recipients in a 9 multi-center Adult to Adult Living Donor Liver Transplantation Cohort Study, graft and patient survival and the development of advanced fibrosis were compared among 181 living donor liver transplant (LDLT) recipients and 94 deceased donor liver transplant (DDLT) recipients. Overall 3-year graft and patient survival were 68% and 74% in LDLT, and 80% and 82% in DDLT, respectively and it was concluded that the 3-year graft and patient survival in HCV-infected recipients of DDLT and LDLT were not significantly different (6).The incidence of HCV recurrence in our studied group was 29.8% for patients who passed time ranging from at least 6 months to 4 years this average percentage of recurrence is not to be considered more than that reported in the literature for cadaveric liver

transplantation if not even less. In another retrospective analysis of 289 HCV-LT (20 LD splits) patients receiving transplants. Patient and organ survival, intensity of HCV recurrence, and fibrosis progression were analyzed with respect to deceased donor (DDLT) or (LDLT). in this patient sample, intensity of HCV recurrence was not increased in LDLT graft recipients compared to full-size recipients. Patient and organ survival were similar. LDLT can therefore be advocated for HCV patients (7). The rate of acute cellular rejection (ACR) and high-degree ACR are decreased in living-related liver transplant recipients than for cadaveric (8). It is also estimated that the number of rejection episodes is actually much less for HCV infected individuals (9). Factors contributing to the recurrence of HCV after LDLT are multiple and include; overweight, alcohol intake and level of immunosuppression. Concerning immunosuppression; keeping appropriate levels is considered as a key factor as low level of immunosuppression would lead to rejection episodes necessitating corticosteroid boluses or other antibodies leading to increased incidence of HCV recurrence, on the other hand high levels of immunosuppression would lead to increased side effects of the immunosuppressive drugs as well as severely depressed immune status also enhancing HCV replication leading to HCV recurrence in the new graft. This is consistent with a universal finding that has emerged over the past decade, that immunosuppression increases the serum level of HCV RNA, and this is particularly true for patients treated with monoclonal antibody preparations and corticosteroids (10-15). In our study we studied the effect of using different calci-neurin inhibitors on HCV recurrence in our study and has been ruled out by a subgroup analysis of patients receiving FK & Basiliximab and another group receiving Neoral & Basiliximab, the incidence of HCV recurrence was 54.5% Vs 60% respectively ($p>0.05$ nonsignificant). Although the use of induction therapy with basiliximab seems to be safe and efficient, its effect on the recurrence of HCV in our study is hazardous. Induction therapy with basiliximab increased HCV recurrence as presented in our study; a 56.3% in the induction group Vs 16.1% in the non-induction group which is statistically a highly significant difference ($P<0.001$). We find that these findings are indirectly proven in more than one study as the effect on the incidence of recurrent hepatitis C is of major concern with any additional immunosuppressive agent used. In two trials, any favorable effect on rejection with basiliximab was smaller in HCV positive patients. The investigators stated that the rate of recurrent hepatitis C at 6 months post-transplantation was 48.4% (16). In summary, our study shows the deleterious effects of using induction therapy with Basiliximab on the recurrence of HCV post LDLT. We demonstrated that the use of the different calci-neurin inhibitors had no effect on HCV recurrence in our studied group. Therefore we recommend limiting the use of basiliximab as induction therapy in cases of HCV patients undergoing LDLT, only for cases whom starting immunosuppression need to be delayed post transplant specially those patients with renal impairment. Specially that the need for induction therapy for fear of rejection, which is generally less in cases of LDLT than that in cases of cadaveric liver transplant.

Corresponding author
Wael Safwat
Theodor Bilharz Research Institute, Cairo, Egypt
waelsafwat@yahoo.com

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