Analysis of Liver Function Test Abnormalities in Kidney Transplant Recipients

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INTRODUCTION AND AIMS: Immunosuppressive agents are associated with specific side effects such as hepatotoxicity, considered as a benign condition and resulting generally in a transitory and small increase in transaminase levels. There are a few series and many case reports including any drug-spesific hepatotoxicity in the literature. Therefore, the objective of this study is to identify the characteristics and consequences of hepatotoxicity episodes, risk factors affecting development of hepatotoxicity and its severity in kidney transplant recipients.

METHODS: The study retrospectively evaluated medical records of adult recipients who performed kidney transplantation from January 2005 to March 2012. Hepatotoxicity episodes were defined in the presence of impairment of liver function tests which responds to drug dose reduction or discontinuation, or treatment of specific cause such as infectious complications. All hepatotoxicity episodes were divided into three groups depending on their ALT levels which was more specific to liver: group 1 with ALT level of upper limit of normal (ULN) to 3 times more than ULN; group 2 with ALT level of >3 to 5 times more than ULN and group 3 with ALT level of >5 times more than ULN.

RESULTS: Of the 281 renal transplant patients 56% were male and the overall mean age were 35.9 years. One hundred-fifty-six episodes of hepatotoxicity occurred in 107 patients following 281 renal transplants, an incidence of 38%. Twenty-nine patients have two episodes and 10 patients have three episodes of hepatotoxicity. The most common cause of liver injury were drugs in all three groups (p=0.005, Table 1). Drug usage (especially, mycophenolate mofetil-MMF, p=0.035) were significantly lower in group 1 than other two groups. Mean hepatotoxic episode occurring time was 5.3±9.2 month (range 1-63) after transplantation. Mean duration was 67.5±94.8 day (range 2-735) for remitting episodes. But 17 episodes remained floating course or not remitted. Attacs duration was significantly shorter in group 1 than others. Patients with hepatotoxicity episodes as compared with those with no hepatotoxicity episodes were as follows: had a high total mortality rate (14% vs. 6.3%, p=0.031), higher positive pretransplant CMV Ig M test (15.2% vs 3.6%, p=0.033), higher first month creatinin value (1.46±0.47 vs. 1.34±0.72, p=0.013); underwent further acute rejection episodes (15.6% vs. 7%, p=0.04); received less cyclosporin/MMF/prednisolone protocol (31.4% vs. 47.7%, p=0.016) and more everolimus/MMF/prednisolone protocol (23.5% vs. 9.4%, p=0.002). No significant difference was observed regarding sex, age, dialysis type and duration, primary disease, positive HBsAg and anti-HCV test, histories of delayed graft function and chronic rejection between both groups. In regression analysis only positive CMV IgM test was independent risk factors for hepatotoxicity (OR 16.86, 95% CI 1.82-155.8; p=0.013). However, receiving cyclosporin/MMF/prednisolone protocol was decreased this risk in that analysis (OR 0.32, 95% CI 0.127-0.83; p=0.02). Liver biopsy showed toxic hepatitis in 2 patient who had severe enzyme elevation. Forty-eight attacks (30.8%) have infectious complications during hepatotoxicity episode. Coexistence of acute rejection was present in 6 hepatotoxicity attacs. Impairment of renal function occurred in 15 attacs (9.7%) and there was no difference between groups.

CONCLUSIONS: We reported here, to the best of our knowledge, the first case series investigating the etiology of hepatotoxicity in kidney transplant recipients. Drug-related hepatotoxicity is more common in renal transplant recipients. However. it has been considered being many causes in reciptients with relapsing episodes.

Table 1: Etiologies of hepatotoxicity in the groups according to liver enzyme levels

Etiology, n(%)	Total (n=156)	Group1 (n=83)	Group 2 (n=34)	Group 3 (n=36)
Drugs	68 (43.6)	27 (32.1)	18 (51.4)	23 (62.2)
MMF	26 (16.6)	9 (10.8)	6 (17.6)	11 (30.5)
Tacrolimus	13 (8.3)	5 (6)	4 (11.4)	4 (10.8)
Cyclosporin	4 (2.6)	2 (2.4)	0 (0)	2 (5.4)
Everolimus	1 (0.6)	0 (0)	1 (2.9)	0 (0)
Sirolimus	1 (0.6)	0 (0)	0 (0)	1 (2.7)
Antibiotics	26 (16.6)	12 (14.3)	7 (20)	7 (18.9)
TMP/SMX	10 (6.4)	5 (6)	2 (5.7)	3 (8.1)
Unknown etiology	63 (40.4)	43 (51.2)	15 (42.9)	5 (13.5)
Sepsis/hypoxy	8 (5.1)	4 (4.8)	2 (5.7)	2 (5.4)
Cytomegalovirus	9 (5.7)	3 (3.6)	0 (0)	6 (16.2)
Hyperlipidemia	4 (2.6)	4 (4.8)	0 (0)	0 (0)
Hepatitis B	2 (1.3)	2 (2.4)	0 (0)	0 (0)
Acute pancreatitis	1 (0.6)	1 (1.2)	0 (0)	0 (0)
Cholelititasis	1 (0.6)	0 (0)	0 (0)	1 (2.7)

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