Immunosuppressive Therapy-Induced Hepatotoxicity in Patients with Aplastic Anemia

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ABSTRACT

Immunosuppressive therapy is a treatment for aplastic anemia patients who are not candidates for hematopoietic stem cell transplantation. The aim of the study to evaluate the frequency and severity of immunosuppressive therapy-induced hepatotoxicity in patients with aplastic anemia. The records of 27 patients with aplastic anemia who had received immunosuppressive therapy were received and determined for evidence of hepatotoxicity. The patients were divided into three groups. Group 1 was treated with antithymocyte/antilymphocyte globulin and cyclosporin A, group 2 received only cyclosporin-A and group 3 was treated with antithymocyte/antilymphocyte globulin + cyclosporin-A and granulocyte macrophage colony-stimulating factor. All patients in group 1 had an initial increase in AST and ALT levels after therapy, but these tests abnormalities returned to normal in each case (p> 0.05). There was no detectable change in AST and ALT levels in group 2 (p>0.05). In group 3, five patients had an increase in ALT and AST levels in the initial several days after therapy was started but the levels gradually returned to normal by the second or third week of therapy.

In conclusion, immunosuppressive therapy-induced hepatotoxicity in patients with aplastic anemia is generally mild and transient but can be fatal.

Key Words: Aplastic anemia, Hepatotoxicity, Immunosuppressive therapy, Liver, Antithymocyte/antilymphocyte globulin.

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INTRODUCTION

Aplastic anemia (AA) is a rare disease characterized by pancytopenia and a hypocellular bone marrow[1]. Bone marrow transplantation (BMT) can cure patients with AA who are eligible for this procedure. Unfortunately most patients are ineligible for BMT because they either lack a histocompatible donor or their advanced age[1,2].

Immunosuppressive therapy is a treatment for patients with AA who are not candidates for bone marrow transplantation[3]. For this purpose either antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) are commonly used either alone or combined with cyclosporin A (Cs-A)[3,4]. Response rates of more than 50% can be achieved when ATG/ALG is used alone or in combination with either androgenic steroids or Cs-A[5-7]. Numerous complications can be attributed to ATG/ALG therapy in patients with AA. These include fever, hypertension or hypotension, allergic reactions, anaphylaxis, hemolysis, pancytopenia and serum sickness disease[3,6,7]. Hepatotoxicity is a rare but important complication[8].

In this manuscript, the frequency and severity of immunosuppressive therapy-induced hepatotoxicity in patients with AA was determined by means of a retrospective review of the records of 27 consecutive cases seen at Hematology and Oncology Department, Medical School, University of Ankara.

MATERIAL and METHODS

The records of 27 patients with AA, who were admitted to the University of Ankara, Hematology and Oncology Department between January 1990 and July 1998 were received. 18 patients (67%) had severe AA while 9 (33%) had non-severe AA. The male to female ratio was 22/5. Their median age was 19 years (14-55 years). Thirteen patients (48.1%) received ATG/ALG + Cs-A (Group 1), 8 patients (29.7%) received only Cs-A (Group 2), and 6 patients (22.2%) received ATG/ALG + Cs-A + granulocyte macrophage colony-stimulating factor (GM-CSF) (Group 3).

Treatment schedules; Horse antilymphocyte globulin or Rabbit antithymocyte globulin, 15 mg/kg/d x 5 (1,2,3,4,5), was given as a slow intravenous (iv) infusion in saline over 6-8 hours after premedication with methylprednisolone 2 mg/kg/d iv. The methylprednisolone was tapered and stopped at day +30. Cs-A was started at a dose of 5 mg/kg/d per oral on day +1 and continued until day +30. GM-CSF was used at a dose of 5 µg/kg/d until the neutrophil count increased above a level of $0.5x10^9$/L.

Liver function tests; Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (gGTP), lactate dehydrogenase (LDH), alkaline phosphatase (AP) and bilirubin levels were measured by the clinical Biochemistry Department of Ankara University on a 24 factor automated chemical analyzer using standard reagents and methods. The normal ranges are 0-40 U/L for AST, ALT, 0-57 U/L for gGTP, 41-117 U/L for AP, 90-230 U/L for LDH, and 0-1.4 mg/dL for bilirubin. Complete blood counts and liver injury tests were performed every 3 days during the first two weeks then one time per week until day +30. Tests were performed at closer intervals when indicated clinically.

All viral disease screening tests were negative (i.e. hepatitis A-IgM, B, C, parvovirus, CMV IgM) before therapy. All patients received oral prophylaxsis consisting of sulfamethoxazole-trimethoprim (800 mg/d-160 mg/d), fluconazole (100 mg/d) and famotidine (40 mg/d).

Statistical analysis; All eligible patients, except one patient who died with acute fulminant hepatic failure before the end of the trial, were included in the analysis. All data were analyzed by Kruskal-Wallis 1-Way Anova, Wilcoxon Matched-Pairs Signed-Ranks and Chi-Square tests.

RESULTS

Overall, the immunosuppressive treatment was tolerated well by each group. There were no serious reactions requiring discontinuation of the various therapeutic modalities. One patient in group 3 developed acute fulminant hepatic failure which may have been due to either a drug-induced reaction or hepatitis G virus (HGV)-induced liver failure. HGV-RNA was detected by polymerase chain reaction (PCR) in her sera. Before the

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initiation of therapy, there were no differences in initial ALT and AST levels (Table 1a, 1b), sex and age among three different treatment groups (p> 0.05).

One patient in group 1 had a baseline levels of AST and ALT 4 and 2 times the normal level, respectively. These tests abnormalities returned to the normal range at the end of second weeks of therapy. In the remaining 12 patients, the serum AST and ALT levels were observed to increase with therapy; a mean rise of 5 IU/L (maximum 20 IU/L) for AST and 15 IU/L (maximum 70 IU/L) for ALT was observed in the first week, and a mean rise of 8 IU/L (maximum 70 IU/L) for AST, 10 IU/L (maximum 25 IU/L) for ALT was observed in the second weeks. These increases were significant for ALT between the first week and second weeks (p< 0.05, p= 0.0499) (Figures 1a, 1b).

There were no remarkable changes in liver injury tests in group 2 (Tables 1a, 1b). AST and ALT levels were in the normal range before therapy. During the first week of therapy, the maximum increase in AST level was 9 IU/L and there was no significant change in ALT level (p> 0.05).

One patient in group 3 had initial baseline levels of AST and ALT 3 and 2 times the normal level, respectively. These levels returned to normal range within second weeks of the initiation of the-

rapy. Four patients in this group experienced an increase in ALT and AST levels 2 days after the initiation of therapy (Figures 1a, 1b), these levels returned to normal range between the second and third weeks of therapy. The remaining one patient, experienced a sharp increase in AST and ALT levels to values of 4796 IU/L and 2837 IU/L respectively (Figure 2). This patient died on the 13th day of therapy with fulminant hepatic failure confirmed by autopsy.

Despite the single case of fulminant hepatic failure in group 3, there were no significant changes in liver injury tests between initial levels and the levels at the end of four weeks among the three different therapeutic groups (p> 0.05) (Tables 1a, 1b).

DISCUSSION

The effects of BMT on the liver are multifactorial and include graft-versus host disease (GVHD), veno-occlusive disease, sepsis (viral, bacterial) and drug toxicity[9]. Immunosuppression is the therapy utilized for AA patients, who lack a human leukocyte antigen (HLA)-identical sibling[1,2]. Immunosuppression has been reported to achieve response rates similar to those BMT, and studies comparing these two treatment modalities have shown equivalent long-term survival rates. However both therapies have many side effects

Table 1a. Statistical analysis of AST levels pre and post-immunosuppressive therapy

Group	Patient number	0 (initial) X ± SD	1. week X ± SD	2. weeks X ± SD	3. weeks X ± SD	4. weeks X ± SD
1	13	62.33 ± 98.06	25.75 ± 10.61	27.0 ± 9.52	26.25 ± 9.96	22.82 ± 8.48
2	8	28.88 ± 14.37	27.25 ± 14.35	25.63 ± 15.54	24.86 ± 9.15	23.50 ± 7.75
3	5	56.0 ± 64.86	76.75 ± 38.32	33.75 ± 25.51	40.0 ± 22.85	38.33 ± 20.26

Table 1b. Statistical analysis of ALT levels pre and post-immunosuppressive therapy

Group	Patient number	0 (initial) X ± SD	1. week X ± SD	2. weeks X ± SD	3. weeks X ± SD	4. weeks X ± SD
1	13	63.25 ± 11.34	48.76 ± 36.17	36.73 ± 40.44	28.4 ± 24.36	19.44 ± 6.56
2	8	22.86 ± 7.94	23.0 ± 11.40	30.63 ± 12.78	26.0 ± 6.0	28.0 ± 6.53
3	5	39.76 ± 16.50	66.26 ± 20.76	83.0 ± 102.04	21.3 ± 15.76	38.0 ± 32.51

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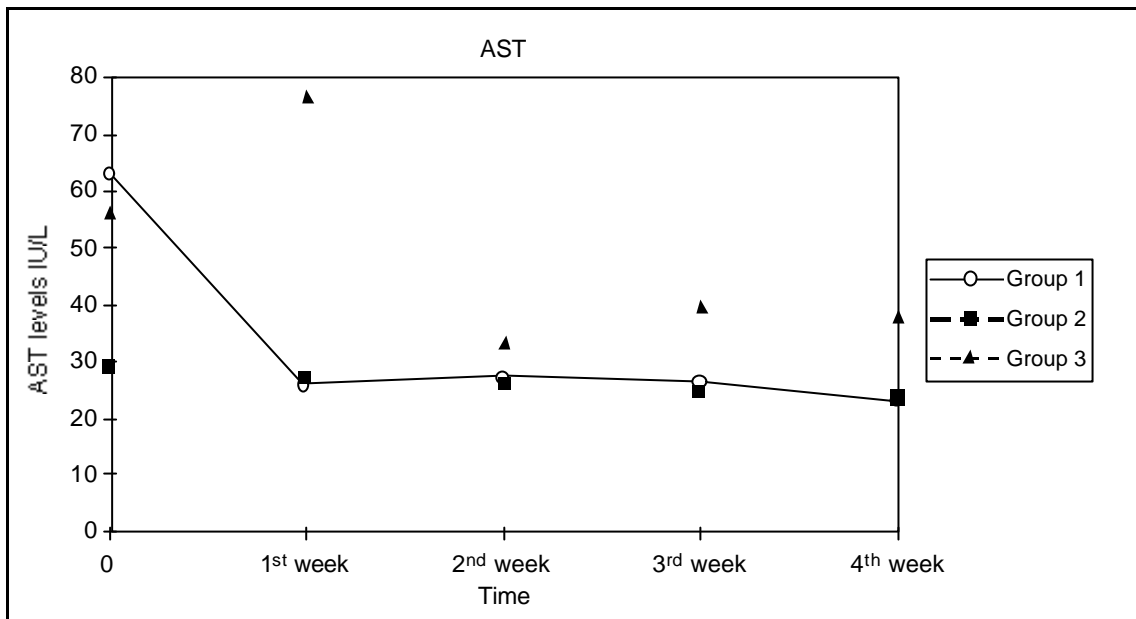Patients with Aplastic Anemia

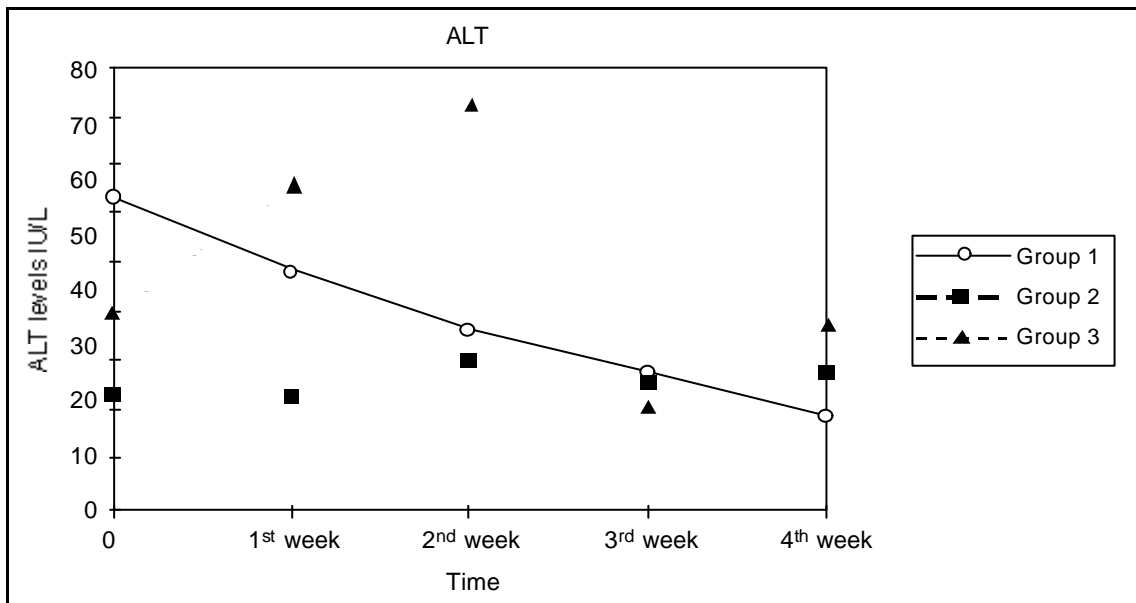Figure 1a. Serum AST levels pre and post-immunosuppressive therapy. Normal range of AST 0-40 IU/L.

Figure 1b. Serum ALT levels pre and post-immunosuppressive therapy. Normal range of ALT 0-40 IU/L.

which include hepatotoxicity[8,10,11].

Drug-induced hepatic injury is the facet of BMT hepatotoxicity of most interest to clinicians. The importance of drug-induced hepatic injury rests on both its frequency and its character. Reactions to drugs account for less than 10% of all cases of apparent hepatitis however drug toxicity can be fatal[12,13]. In this report, an experience with hepatotoxicity in patients with AA treated with ATG/ALG either alone or in combination with Cs-A and/or GM-CSF is described. Except for one death due to fulminant hepatic failure possibly
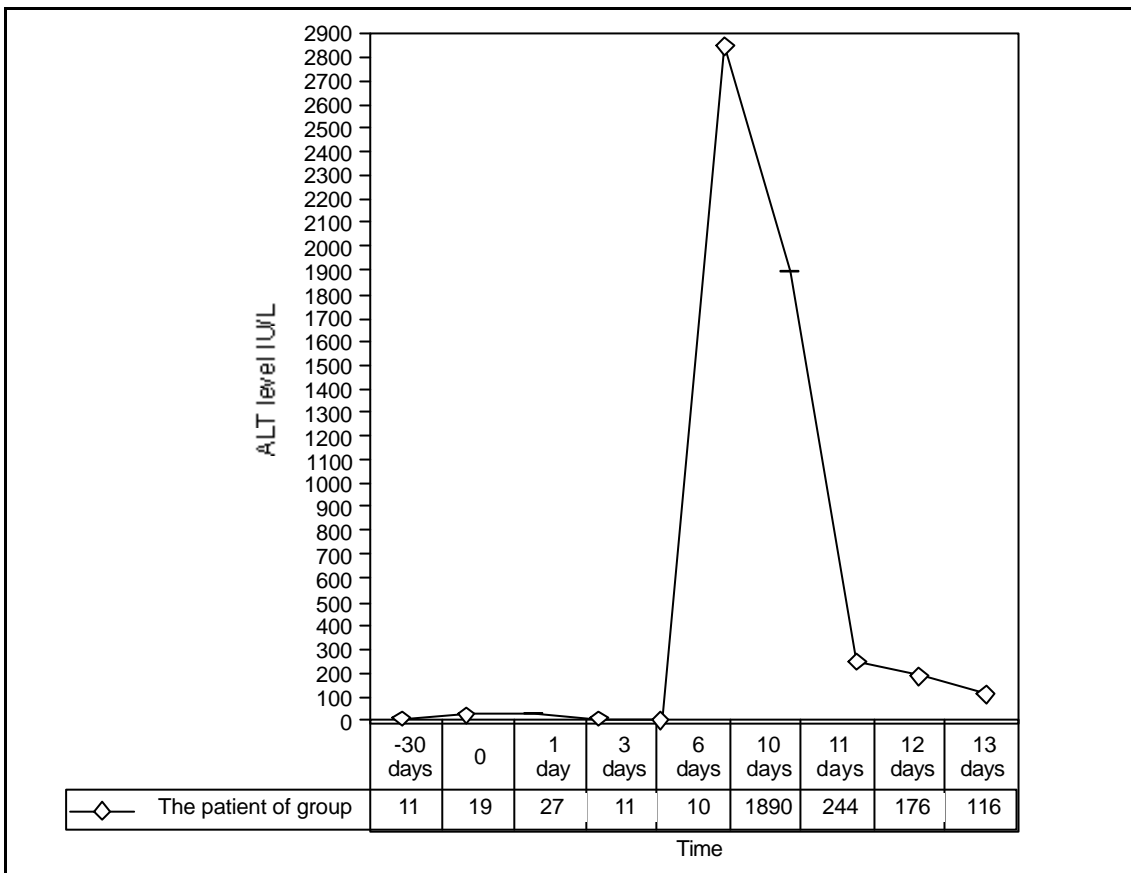
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Figure 2. The characterization of ALT level of patient who died during immunosuppressive therapy.

	-30 days	0	1 day	3 days	6 days	10 days	11 days	12 days	13 days
The patient of group	11	19	27	11	10	1890	244	176	116

Time

due to HGV, there were no major side effects whether these agents were given alone or together; however some patients complained of chills and fever during their ALG/ATG infusion.

With the use of potentially hepatotoxic drugs, hepatic necrosis, cholestasis, sinusoidal and endothelial damage can be observed[12,13]. The principal characteristic of drug related hepatotoxicity is the normalization of liver injury tests following the cessation of drug. Killick et al, reported only transient increases in ALT and AST levels in aplastic anemia patients treated with ATG[8]. Similarly in the present study, only mild and transient increases in levels of ALT and AST were observed in most patients receiving ATG/ALG and Cs-A or in combination with GM-CSF in the first two weeks of therapy. There was no significant differences in liver injury test levels among the three

groups studied despite the inclusion of a case of fulminant hepatic failure in group 3 (p> 0.05).

The factors that lead to hepatotoxicity in cases with disease such as AA are multifactorial and includes infections, steroids and Cs-A. The increased risk of infection in these patients is due in large measure to the immunosuppressive therapy they receive[14]. In the present study, all 27 patients received prophylaxis for opportunistic infections. Each of these drugs is known to be potentially hepatotoxic. Reactivation of viruses, especially latent viral infections such as hepatitis B and herpes viruses, has been reported after immunosuppressive therapy[9,15,16]. In the present study, only one patient in group 3 who was HGV-RNA positive by PCR experience fulminant hepatic failure. Cs-A can cause hepatotoxicity but the toxicity is usually choleostatic rather than hepatic

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character[17]. No increase in serum bilirubin level occurred in the patients receiving Cs-A either alone or in combination. Importantly Cs-A blood levels were consistently in the normal range during the period of Cs-A treatment.

The one patient in group 3 who died during immunosuppression therapy was a 17 years old female with severe aplastic anemia, who had no HLA-identical donor for BMT. She received ALG + Cs-A + GM-CSF and on the 9th treatment day, she complained of anorexia, fatigue, and right upper quadrant abdominal pain. She was afebrile, mildly confused and jaundiced. Her physical examination revealed mild hepatomegaly, but no stigmata of chronic liver disease. Her liver injury tests dramatically worsened in a few days (Figure 2). Supportive therapy was initiated for fulminant liver failure and her immunosuppressive therapy was discontinued. Her clinical state worsen over the next 4 days and she died on 13th day of treatment. Post-mortem liver examination documented submassive necrosis. HGV-RNA positivity was detected by PCR in her sera before she died. Recently, some investigators have suggested that HGV is not always an innocent virus[18,19]. The role of HGV in fulminant hepatitis as well as in the etiology of aplastic anemia remains controversial. Little is known about the relationship of HGV and the clinical course of fulminant and chronic viral hepatitis[18-20]. HGV may play role in the etiology of these diseases.

In conclusion, immunosuppressive drug-induced hepatotoxicity in patients with AA usually is mild and transient, but can be fatal. These results suggest that hepatotoxicity is not a major problem following immunosuppressive therapy of patients with AA. The role of HGV and HGV plus immunosuppression in such cases particularly those with FHF (rare) needs to be assessed with more experience.

ACKNOWLEDGMENTS

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