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**Aplastic anemia and severe pancytopenia during treatment with peg-interferon, ribavirin and telaprevir for chronic hepatitis C**

Lens S *et al*. Aplastic anemia during HCV antiviral therapy

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**Abstract**

Telaprevir and Boceprevir are the first direct acting antivirals approved for chronic hepatitis C in combination with perginterferon alfa and ribavirin. Pancytopenia due to myelotoxicity caused by these drugs may occur but severe hematological abnormalities or aplastic anemia (AA) have not been described. We collected all cases of severe pancytopenia observed during triple therapy with telaprevir in four Spanish centers since the approval of the drug (2011). Among 142 cirrhotic patients receiving treatment, 7 cases of severe pancytopenia (5%) were detected and three of them were consistent with the diagnosis of AA. Mean age was 59 years, five patients had compensated cirrhosis and two patients had severe hepatitis C recurrence after liver transplantation. Severe pancytopenia was diagnosed a median of 10 weeks after the initiation of therapy. Three patients had pre-treatment hematological abnormalities related to splenomegaly. In six patients, antiviral treatment was interrupted at the onset of hematological abnormalities. Two patients died due to septic complications and one patient due to acute alveolar haemorrhage. The remaining patients recovered. Severe pancytopenia and, especially, aplastic anemia are not rare during triple therapy with telaprevir in patients with advanced liver disease. Close monitoring is imperative in this setting to promptly detect serious hematological disorders and to prevent further complications.

**Key words:** Aplastic anemia; Hepatitis C; Telaprevir; Interferon; Protease inhibitors

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**Core tip:** The addition of new directly acting antivirals Telaprevir and Boceprevir clearly improved sustained virological response rates in patients with chronic hepatitis C. However, these combinations have also increased the risk for serious adverse events, especially in patients with advanced liver fibrosis. We describe the development of severe pancytopenia and, aplastic anemia during triple therapy with telaprevir in patients with advanced liver disease (before or after liver transplantation). Close monitoring is imperative in this setting to promptly detect serious hematological disorders and to prevent further complications.

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**Introduction**

The addition of new directly acting antivirals (DAAs) Telaprevir and Boceprevir clearly improved sustained virological response (SVR) rates in patients with chronic hepatitis C[1-5]. However, these combinations have also increased the risk for serious adverse events (SAEs). One of the most common adverse events associated to triple therapy compared to standard peg-interferon and ribavirin (PR) regimens is anemia[6]. Interferon- related bone marrow suppression and ribavirin related haemolytic anemia are common and may lead to dose-reduction, especially in patients with baseline cytopenia[7]. Nonetheless, very few cases of severe pancytopenia and only one case of aplastic anemia related to interferon therapy have been reported in patients with chronic hepatitis C virus (HCV)[8,9]. Thus, severe hematological disorders appear to be anecdotic since a great number of patients have been treated with these drugs during the last decades. As far as we know, cases of aplastic anemia related to telaprevir or boceprevir combination therapy have not been reported. Instead, a case of successful triple therapy in a patient with severe aplastic anemia has been recently reported[10].

We describe here 7 cases of severe pancytopenia in patients receiving antiviral treatment with PR and telaprevir, three of them being consistent with the diagnosis of aplastic anemia (AA).

**CASE REPORT**

***Case 1***

This patient was a 51 year-old woman with genotype 1b HCV related cirrhosis. She had stable neutropenia (1500 cells/μl) and thrombocytopenia (74 x 109/L) that were likely related to portal hypertension (hepatic venous portal pressure gradient (HVPG) of 16 mmHg). Esophageal varices were not found in upper gastrointestinal endoscopy. She had no comorbidities and she did not take any medications. Viral load (VL) was undetectable at week 4 of triple therapy including telaprevir. At this time, blood analysis revealed worsening of neutropenia (1000 cells/μl), thrombocytopenia (42 x 109/L) and a decrease of 2.5 g/dl in haemoglobin (Hb) level, leading to interferon and ribavirin dose reduction. One week later, she complained of worsening of general condition, epistaxis, and mild rash. Blood tests revealed severe pancytopenia (Table 1). The patient was admitted to the hospital; antiviral therapy was immediately interrupted and blood and platelet transfusions were administered. In spite of supportive blood transfusion and granulocyte colony-stimulating factor (GCSF) hematological abnormalities did not improve. A bone marrow aspirate showed a leucocyte population formed by lymphocytes (41%) and normal phenotypic plasmatic cells (55%) with absence of neutrophils. Bone marrow biopsy was compatible with AA (Figures 1 and 2). Other acquired causes of bone marrow failure such as myelodisplasic syndromes, leukemia, megaloblastic anemia, paroxysmal nocturnal hemoglobinuria and viral hemophagocytic syndrome were excluded. Due to the lack of improvement of hematological parameters and the contraindication of bone marrow transplantation, cyclosporine was started with no improvement. The patient developed pulmonary aspergillosis and subsequently presented progressive liver and renal failure and died 50 days after admission.

***Case 2***

This patient is a 56 year old woman with HCV genotype 1a related cirrhosis that was diagnosed 6 years earlier by liver biopsy and remained compensated. She was on oral therapy for diabetes mellitus. Two days after the initiation of triple therapy with telaprevir she developed a grade I micropapular rash which was successfully treated with topical corticoids and anti-histaminics. At week 4 of therapy she complained of fever, odynophagia and cough. Physical examination showed an erythematous tonsillitis with candidiasic lesions. Blood tests showed a total leukocyte count of 570 cells/μl with 0% neutrophils, 19 x 109/L platelets, 7 g/dl of Hb, and 0.1% reticulocytes (Table 1). The chest X ray was normal. The patient was admitted to hospital and antiviral therapy was withdrawn. A bone marrow biopsy showed marked hypocellularity without morphologic abnormalities, consistent with AA. Supportive treatment with erythropoietin (EPO), GCSF and blood and platelet transfusion was initiated. Oral candidiasis by *Candida albicans* was successfully eradicated. Two months later the patient had fully recovered from of hematological abnormalities.

***Case 3***

This patient was a 67 year old woman with HCV genotype 1a compensated cirrhosis, autoimmune hypothyroidism, arterial hypertension, and well controlled diabetes mellitus. Concomitant medications were metformin, levothyroxin, atenolol and eprosartan. Four weeks after initiation of antiviral therapy with PR and telaprevir, VL was undetectable. There was an Hb concentration decrease of 5 g/dl from baseline and a blood transfusion was administered at this time. Ribavirin dose was adjusted and treatment with EPO was initiated. Three weeks later she was admitted to Intensive Care Unit with the diagnosis of septic shock requiring vasoactive drug support and severe pancytopenia. Antiviral therapy was stopped at admission. Staphylococcus aureus meticillin-sensitive was isolated in blood cultures within 48 h and specific antibiotic therapy was started (cloxacilin and piperacillin-tazobactam). Despite extensive investigations the source of the infection was not identified. Pancytopenia progressively worsened (Table 1). The patient developed renal failure needing haemodialysis as well as liver failure with bilirubin increasing up to 18 mg/dl and ascitic decompensation. The patient presented a multiorgan invasive zygomycosis and died one month after admission. Necropsy confirmed AA with severe hypocelullarity in the bone marrow.

***Case 4***

The patient was a 62 year-old woman with HCV genotype 1b cirrhosis. She had durable neutropenia (about 900 cells/μl) possibly related to hyperesplenism due to portal hypertension (HVPG 8 mmHg). Upper gastrointestinal endoscopy detected a small oesophageal varicose vein. She did not have co morbidities and did not take medications. VL was undetectable at week four of triple therapy with telaprevir. At this point total neutrophil and platelet counts were 700 cells/μl and 47 x 109/L, respectively. One week later she was admitted to the hospital because of fever and chills lasting 48 h. The chest ray showed a right inferior lobe pneumonia and broad spectrum coverage antibiotic therapy was started. Blood tests disclosed severe pancytopenia (Table 1). Antiviral therapy was interrupted and supportive treatment with red blood cell and platelet transfusion was initiated. Seventy-two hours after admission, she suddenly presented a massive hemoptysis with alveolar haemorrhage. Despite orotraqueal intubation and mechanical ventilation the patients suffered a cardiac arrest that was not recovered. Necropsy was not performed.

***Case 5***

This patient is a 68 year old woman with HCV genotype 1b related cirrhosis and cryoglobulinemia. She had no comorbidities and she did not take any medications. VL was undetectable at week 4 of triple therapy with telaprevir. Patient was hospitalized at week 8 due to acute pyelonephritis by *Escherichia coli*. Infection resolved after 2 wk under intravenous antibiotic therapy. Because of grade 3 anemia the patient needed a blood transfusion on week 12, and treatment with EPO and ribavirin dose reduction were required at this time. The patient completed 12 wk of telaprevir therapy and then continued on treatment with PR. During the following 4 wk, the patient developed severe pancytopenia (Table 1) in spite of supportive treatment with transfusions, EPO and GCSF administration. Reticulocyte count was < 1% x 109/L. Other causes of pancytopenia were ruled out. The patient continued on antiviral therapy until week 48, at reduced doses of both PR. She achieved SVR and is currently recovering from the hematological disorder.

***Case 6***

This patient is a 51-year old man who underwent orthotopic liver transplantation (LT) 24 mo before because of advanced HCV genotype 1b cirrhosis. Immunosuppressive therapy consisted in tacrolimus monotherapy with stable levels and no dose modifications during the previous months. He was also taking statins for hypercholesterolemia. No other comorbidities or medications were present. The patient developed HCV recurrence with severe liver injury at 21 mo after LT, as indicated by cholestasis, high VL (4 x 106 IU/mL) and increasing transient elastography values (14kPa). The HVPG value was 8.5 mmHg, and a transjugular liver biopsy showed necroinflammatory activitiy and periportal fibrosis (F2) in METAVIR scale but no signs of rejection. At week 16 of triple therapy with telaprevir, 4 wk after telaprevir was stopped, he presented with grade 3 anemia, neutropenia and severe thrombocytopenia. Antiviral therapy was withdrawn and blood and platelet transfusion were administered (Table 1). Supportive care with EPO and GCSF was maintained for 3 additional months. The patient achieved SVR despite early discontinuation of antivirals, and he also recovered from the hematological abnormalities.

***Case 7***

This patient is a 63 year old woman whose liver histology showed advance fibrosis (F3) 18 mo after LT. She had a genotype 1b infection, viral load was 2 x 106 IU/L, and ALT and AST values were 235 and 536 IU/L respectively. Immunosuppressive treatment consisted of tacrolimus and low-dose prednisone. She had developed diabetes mellitus after LT and was receiving insulin therapy. At the time when triple therapy with PR and telaprevir was initiated, she presented a stable mild thrombocytopenia of 78 x 109/L. At week 4 of therapy, there was a marked decrease of neutrophils (500 cells/μl) along with anemia (Hb 10 g/l) and a further decrease in platelet count (50 x 109/L). The VL was undetectable. Doses of PR were adjusted and supplementary therapy with EPO and GCSF was given. Despite these measures, the neutrophil count continued decreasing and antiviral therapy was interrupted at week 6 (Table 1). One month later the hematological abnormalities disappeared and this was followed by SVR in spite of early discontinuation of therapy.

**Discussion**

The approval of first generation protease inhibitors (PIs), boceprevir and telaprevir, has been a major step forward in the treatment of chronic hepatitis C[1,2,4,5]. Beyond efficacy results, PIs-based regimens in real life compensated cirrhosis may be associated with SAEs such as severe infections (4%-6%), clinical decompensation (3%-4%) and even death. These events were not reported in the registration trials possibly because patients included in these studies were mostly very well compensated cirrhotics without significant portal hypertension. Indeed, a low platelet count was an exclusion criteria (< 90 x 109/L for telaprevir and < 100 x 109/L for boceprevir) in these trials. The results of triple therapy in real life cirrhotic patients demonstrated that a low platelet count (< 100 x 109/L) and a low serum albumin (< 35 g/L) were strong predictors of severe complications. Importantly, the risk for severe complications was 44% in patients with both factors as compared to 3.4% in patients with normal platelet and albumin values[11].

The mechanism of hematological toxicity during triple therapy is not still completely understood, but is probably related to the concomitant administration of all three drugs. Interferon results in bone marrow suppression and ribavirin leads to haemolysis while PIs may cause direct bone marrow toxicity (as suggested in a few reports in the setting of HIV infection[12,13]) in patients with portal hypertension or advanced cirrhosis. Finally, the risk of hematological abnormalities could be also influenced by genetic factors[14].

Severe AA is defined by a bone marrow cellularity < 25%, or 25%-50% with < 30% residual haematopoietic cells, and at least 2 of the following data: neutrophils < 0.5 cells/μl, platelets < 20 x 109/L and low reticulocyte count. The overall incidence of this disease is low, as it is estimated to occur only in 2-4 million people per year[15]. Among currently licensed drugs which have been associated with aplastic anemia there are antibiotics, anti-inflammatory drugs and anticonvulsants[16].

Severe hypocellular bone marrow related to interferon administration has been reported not only in the setting of HCV infection[8,9]. However taking into account the huge number of patients treated with this drug worldwide, the incidence of this adverse event appears to be extremely low. Indeed, in our center, among 1700 HCV patients treated with PR therapy in the last decades, there has been no case of AA. The only reported case in literature is a non-cirrhotic 46-year-old man who developed AA 4 months after the initiation of PR therapy and presented a fatal outcome despite bone marrow transplantation[8].

Among 142 cirrhotic patients receiving treatment in four Spanish centers since the approval of the triple therapy (2011), 7 cases of severe pancytopenia (5%) were detected and three of them accomplished the diagnostic features consistent with AA (2%). Mean age was 59 years, 5 were Child A cirrhotics and two had severe HCV recurrence after LT. Mean liver stiffness value was 18 kPa, three patients had portal hypertension (range: 8.5-16 mmHg) and 3 patients presented pre-treatment abnormal hematological values possibly related to splenomegaly (Table 1). All patients were closely monitored from the beginning of treatment (at least biweekly) and PR dose adjustments were made depending on hematological values. Severe pancytopenia diagnosis was made at a median of 10 wk after telaprevir initiation and antiviral therapy was interrupted at the time of the diagnosis in all cases but one (case 5). At diagnosis, MeDRA classification of adverse events was > 3 in all cases (severe or medically significant but not immediately life-threatening with hospitalization indicated).

Importantly, when these patients were offered triple therapy, data on predictive factors associated to severe complications were not yet available. However, when retrospectively analysing if these patients would have been candidates for antiviral treatment with telaprevir, only case 1 would have been excluded due to the presence of both, thrombocytopenia and hypoalbuminemia (case 1).

Three patients accomplished diagnostic features of AA (cases 1-3). In case 3, AA developed during septic shock and antibiotic treatment, thus, an influence on the development of bone marrow toxicity cannot be disregarded. In the remaining patients, other potential causes of AA were excluded by anamnesis and laboratory tests. Bone marrow biopsy histology revealed hypocellularity and discarded an infiltrative disease (Figures 1 and 2).

Despite all patients were diagnosed very early and received support in referral centers; two patients presented septic complications and deceased in context of multiorgan failure and one patient presented a massive hemoptysis not recovered despite vital support measures.

In conclusion, hematological adverse events are frequent during antiviral therapy with protease inhibitors in chronic hepatitis C. A specialised centre with expertise should be contacted soon in order to start measures aimed at obtaining the best supportive care and exclude other possible causes of pancytopenia. Although AA is a rare condition, it has now been diagnosed during triple therapy with telaprevir in patients with advanced liver disease. Close monitoring of hematological tests is advised during treatment and therapy should be promptly interrupted in case of a decrease of the three hematopoietic series to prevent the establishment of AA and its complications.

**COMMENTS**

***Case characteristics***

Seven cases of severe pancytopenia were detected and three of them accomplished the diagnostic features consistent with aplastic anemia (AA) during triple therapy with telaprevir. Mean age was 59 years, 5 were Child A cirrhotics and two had severe hepatitis C virus (HCV) recurrence after liver transplantation. Mean liver stiffness value was 18 kPa, three patients had portal hypertension (range: 8.5-16 mmHg).

***Clinical diagnosis***

Severe pancytopenia diagnosis was made at a median of 10 wk after telaprevir initiation

***Differential diagnosis***

Other causes of hematological disorders were discarded (drug toxicity, vitamin deficiency, bone marrow infiltration, malignancy).

***Laboratory diagnosis***

Severe AA was defined by a bone marrow cellularity < 25%, or 25%-50% with < 30% residual haematopoietic cells, and at least 2 of the following data: neutrophils < 0.5 cells/ul, platelets < 20 x 109/L and low reticulocyte count. The remaining cases had severe pancytopenia (hemoglobin levels < 10 g/dl, neutrophils < 0.75 cells/ul and platelets < 50 x 109/L)

***Pathological diagnosis***

Bone marrow biopsy histology revealed hypocellularity and discarded an infiltrative disease.

***Treatment***

Early discontinuation of therapy after diagnosis. Supportive care with G-CSF and blood and platelet transfusion was administered. One patient received cyclosporine.

***Related reports***

Interferon- related bone marrow suppression and ribavirin related haemolytic anemia are common and may lead to dose-reduction, especially in patients with baseline cytopenia. Nonetheless, very few cases of severe pancytopenia and only one case of AA related to interferon therapy have been reported in patients with chronic hepatitis C infection

***Term explanation***

The addition of a protease inhibitor to antiviral treatment may induce bone-marrow toxicity, especially in patients with advanced liver disease.

***Experiences and lessons***

In conclusion, hematological adverse events are frequent during antiviral therapy with protease inhibitors in chronic hepatitis C. A specialized centre with expertise should be contacted soon in order to start measures aimed at obtaining the best supportive care and exclude other possible causes of pancytopenia. Although AA is a rare condition, it has now been diagnosed during triple therapy with telaprevir in patients with advanced liver disease. Close monitoring of hematological tests is advised during treatment and therapy should be promptly interrupted in case of a decrease of the three hematopoietic series to prevent the establishment of AA and its complications.

***Peer-review***

The authors presents seven cases of severe pancytopenia (three of them with AA) occurred in patients with HCV related cirrhosis during triple therapy (peginterferon + ribavirin + telaprevir). The adverse effects associated with triple therapy are common and well-known

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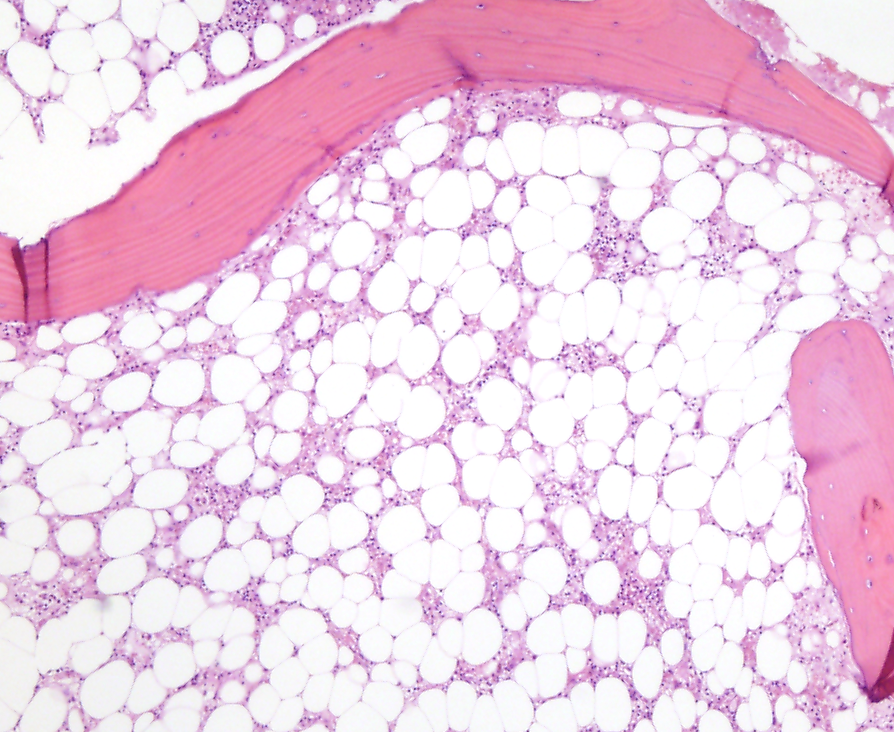
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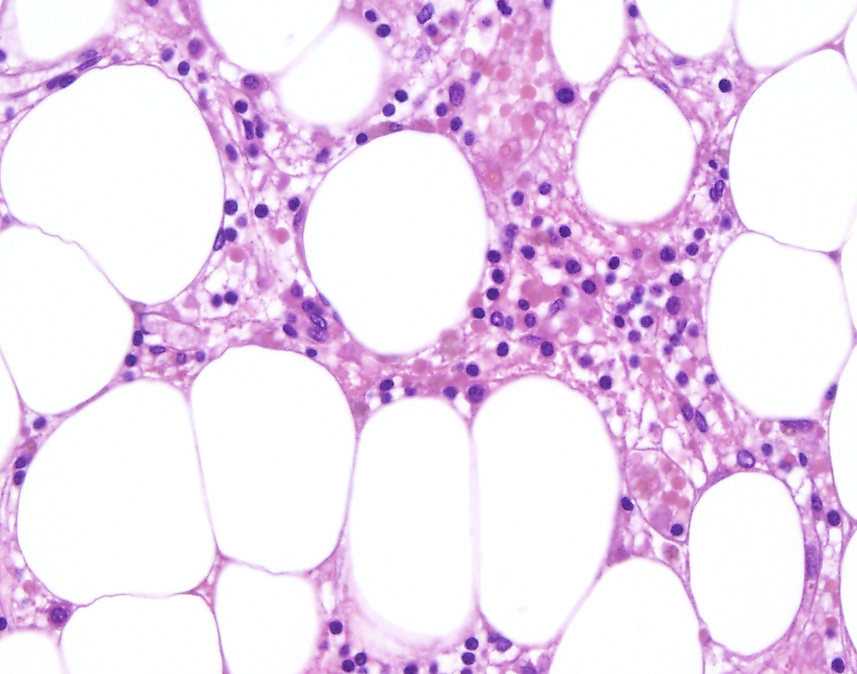
**Table 1 Liver function and blood tests at baseline and at the development of severe pancytopenia and final outcome**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Case 1** | **Case 2** | **Case 3** | **Case 4** | **Case 5** |  | **Case 6**  **(LT)** | **Case 7**  **(LT)** |
| **Features at baseline** |  | | | | | | | |
| Haemoglobin (g/dL) | 14.3 | 14.2 | 12.9 | 13.5 | 13.4 |  | 13.9 | 14 |
| Neutrophils (mm3) | 1500 | 1320 | 1900 | 900 | 3810 |  | 2880 | 1700 |
| Platelets (mm3) | 74000 | 96000 | 108000 | 101000 | 199000 |  | 102000 | 78000 |
| ALT (IU/L) | 59 | 77 | 46 | 96 | 77 |  | 120 | 536 |
| Bilirubin (mg/dl) | 1.3 | 0.93 | 0.6 | 1.1 | 0.5 |  | 1.4 | 1.2 |
| Albumin (g/dl) | 32 | 47 | 37 | 40 | 45 |  | 35 | 36 |
| INR | 1.1 | 1.1 | 1 | 1 | 1 |  | 1.1 | 1.28 |
| Liver stiffness (kPa) | 50 | 10.8 | 16 | 11 | 16.8 |  | 14.2 | 12 |
| HVPG (mmHg) | 16 | - | - | 8.5 | - |  | 8.5 | - |
| Child-Pugh score | 6 | 5 | 5 | 5 | 5 |  | 6 | 5 |
| **Features at diagnosis of pancytopenia** |  |  |  |  |  |  |  |  |
| Triple therapy (wk) | 10 | 4 | 7 | 5 | 16 |  | 16 | 8 |
| Haemoglobin (g/dl) | 7.5 | 7 | 7.8 | 7.6 | 7.2 |  | 7.9 | 8.5 |
| Neutrophils (cells/ul) | 400 | 0 | 250 | 200 | 400 |  | 400 | 300 |
| Platelets (109/L) | 5000 | 19000 | 2400 | 23000 | 12000 |  | 9000 | 30000 |
| Reticulocytes (109/L) | 0.2% | 0.1% | 0.6% | - | <1% |  | <1% | - |
| Bone Marrow Biopsy | Yes | Yes | Yes | - | - |  | - | - |
| **Specific treatment** |  | | | | | | | |
| Treatment interruption | Yes | Yes | Yes | Yes | No |  | Yes | Yes |
| Blood transfusion (units) | 14 | 7 | na | 6 | 20 |  | 10 | 0 |
| EPO (days of therapy) | 30 | 60 | 60 | 6 | 240 |  | 90 | 30 |
| GCSF (days of therapy) | 30 | 60 | 30 | 6 | 90 |  | 90 | 45 |
| **Outcome** | Death | Recovered | Death | Death | Recovered |  | Recovered | Recovered |

LT: Liver transplantation; ALT: Alananin-aminotransferase; INR: International normalized ratio; HVPG: Hepatic venous pressure gradient; AA: Aplastic anemia; EPO: Erythropoietin; GCSF: Granulocyte colony stimulating factor; NA: Not available.



**Figure 1 Bone marrow section showing a marked reduction in hemopoietic precursors which are mainly replaced by fat (HE 200 x).**



**Figure 2 Hematopoietic cells replaced by fat vacuoles and a variable inflammatory infiltrate composed of lymphocytes and plasma cells is observed.** No megakaryocytes are present (HE 400 x).