Severe immune thrombocytopenia after peg-interferon-alpha2a, ribavirin and telaprevir treatment completion: A case report and systematic review of literature

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Abstract

Mild to moderate autoimmune thrombocytopenia (AITP) is a common finding in patients receiving interferon-based antiviral treatment, due to bone marrow suppression. Here we report the case of a patient with chronic genotype 1b hepatitis C virus (HCV) infection treated with pegylated-interferon alpha-2a, ribavirin and telaprevir for 24 wk; the patient developed severe AITP three weeks after treatment withdrawal. We performed a systematic literature search in order to review all published cases of AITP related to HCV antiviral treatment. To our knowledge, this is the second case of AITP observed after antiviral treatment withdrawal. In most published cases AITP occurred during treatment; in fact, among 24 cases of AITP related to interferon-based antiviral treatment, only one occurred after discontinuation. Early diagnosis of AITP is a key factor in order to achieve an early interferon discontinuation; in the era of new direct antiviral agents those patients have to be considered for interferon-free treatment regimens. Prompt prescription of immuno-suppressant treatment (i.e., corticosteroids, immunoglobulin infusion and even rituximab for unresponsive cases) leads to favourable prognosis in most of cases. Physicians using interferon-based treatments should be aware that AITP can occur both during and after treatment, specially in the new era of interferon-free antiviral treatment. Finally, in the case of suspected AITP, presence of anti-platelet antibodies should be checked not only during treatment but also...
We describe the case of a 68-year-old female patient affected by genotype 1b chronic HCV infection (on histology, fibrosis staging F3 according to Metavir); the patient reported a partial response (fall of 4 log10 HCV-RNA) to a previous course of therapy with Peg-IFNα-2a plus RBV and, in February 2012, started treatment with Peg-IFNα-2a (180 mcg/wk) plus RBV (1200 mg/d) and telaprevir (2250 mg/d during the first 12 wk).

Before starting treatment the patient had normal laboratory tests, in particular: haemoglobin 14 g/dl, white blood cell count 6.840/mmc, platelet count 155.000/microl, aspartate aminotransferase (AST) 32 IU/L, alanine aminotransferase (ALT) 52 IU/L, γ-glutamyl transpeptidase 48 IU/L, total bilirubin 0.89 mg/dL, albumin 4.1 g/dL, gamma-globulin 1550 mg/dL, HCV-RNA 256665 IU/mL, thyroid stimulating hormone 2.08 microU/mL; anti-mitochondrial antibodies, anti-smooth muscle antibodies, anti-thyroid autoantibodies were negative while anti-nuclear antibodies were found positive at a titer of 1:80 with speckled pattern. Anti-platelet antibodies were not assessed. HCV-RNA level decreased rapidly and became undetectable after 2 wk of treatment (-5.4 log UI/mL HCV-RNA in 2 wk). After completing the 12-wk course of triple therapy, the patient continued Peg-IFNα-2a and RBV for other 36 wk.

During treatment, the patient developed severe anemia without clinical signs of blood loss that required two blood transfusions and then therapy with erythropoietin 40000 U/wk for 14 wk.

At the end of the treatment, laboratory values showed: HCV RNA not detectable, normal ALT and AST, hemoglobin 11 g/dl, platelets 115.000/mmc, white blood 2.560/mmc, gamma-globulins 1280 mg/dL.

Three weeks after treatment withdrawal, an episode of gingival bleeding occurred; laboratory finding showed severe thrombocytopenia (1.000/microl) with normal white and red blood cells count; liver and kidney function and coagulation tests were normal. Anti-platelets auto-antibodies, both immunoglobulin M (IgM) and IgG, were found positive, while anti-nuclear antibodies were found positive, as well direct Coomb’s test and irregular antibodies against erythrocytes were negative. Anti-nuclear antibodies were still positive with a speckled pattern. Antibodies anti-*Helicobacter pylori* were negative.

Clinical and laboratory findings were consistent with the diagnosis of AITP; therefore, intravenous methylprednisolone 60 mg/d was started for one week, followed by 30 mg/d of oral prednisone, gradually tapered for three months. No further bleeding and a gradual increase in platelet count were observed; after one week of treatment, platelet count was 40.000/microl. After eight weeks, platelet count was within normal range (211.000/microl), anti-platelet as well as antinuclear antibodies became negative and HCV-RNA was persistently undetectable (the patient achieved a sustained virological response).

**INTRODUCTION**

Presence of autoimmune thrombocytopenia (AITP) could be directly related to hepatitis C virus (HCV) infection, even in early stages of the disease. To date, AITP was not considered an absolute contraindication for interferon-based antiviral treatment and usually resolves after virus clearance[1,2]; however, with the registration of interferon-free regimen, patients with severe thrombocytopenia should be considered for all-or-nothing direct antiviral agents therapy.

On the other side, mild to moderate thrombocytopenia could be observed in patients receiving antiviral treatment with interferon alpha, due to bone marrow suppression[3]. However, severe life-threatening immune thrombocytopenia has rarely been associated with interferon treatment[4-26]. Finally, thrombocytopenia is a common finding in liver cirrhosis, usually related to congestive splenomegaly and to inadequate liver thrombopoietin synthesis[27].

We present a case of a chronic HCV infected patient in which severe AITP occurred 3 wk after pegylated-interferon (Peg-IFNα-2a, ribavirin (RBV) and telaprevir treatment completion.

**CASE REPORT**

We describe the case of a 68-year-old female patient affected by genotype 1b chronic HCV infection (on histology, fibrosis staging F3 according to Metavir); the patient reported a partial response (fall of 4 log10 HCV-RNA) to a previous course of therapy with Peg-IFNα-2a plus RBV and, in February 2012, started treatment with Peg-IFNα-2a (180 mcg/wk) plus RBV (1200 mg/d) and telaprevir (2250 mg/d during the first 12 wk).

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**DISCUSSION**

This is the second case of AITP occurred after Peg-IFN and RBV treatment completion; generally, this side...
Table 1 Literature review and summary of all published cases of interferon-induced autoimmune thrombocytopenia for hepatitis C virus infection

| Ref. | Sex | Age | HCV genotype | Antiviral therapy | Occurrence of AITP | Clinical outcome |
|------|-----|-----|--------------|------------------|-------------------|-----------------|
| de Manuel Moreno et al[9] | F | 46 | 1b | Peg-IFNα-2b + RBV | 12 wk | CR (treated with Rituximab) |
| Kim et al[6] | F | 72 | NR | Peg-IFNα-2a | 120 wk | Corticosteroids responsive |
| Li et al[10] | F | 54 | 1b | Peg-IFNα-2a + RBV | 12 wk | CR |
| Eleftheriou et al[11] | M | 27 | NR | Peg-IFNα-2b + RBV | 24 wk after therapy discontinuation | CR |
| Huang et al[12] | F | 48 | 2 | Peg-IFNα-2a + RBV | 1 wk | Corticosteroids responsive |
| Naz et al[13] | F | 60 | NR | Peg-IFNα-2b + RBV | 7 wk | CR (treated with Ursodesoxycholic acid) |
| Enomoto et al[14] | F | 69 | 1b | Peg-IFNα-2b + RBV | 12 wk | Corticosteroids responsive |
| Carnero-Fernández et al[15] | M | 20 | NR | Peg-IFNα-2b + RBV | 20 wk | CR (treated with ß2 immunoglobulin) |
| Alves Couto et al[16] | M | 44 | NR | Peg-IFNα-2b + RBV | 16 wk | CR |
| Weitz et al[17] | F | 43 | 1b | Peg-INF + RBV | 48 wk | CR (treated with Rituximab) |
| Lambotte et al[18] | F | 73 | 1b | Peg-IFNα-2a + RBV | 8 wk | CR |
| Nakajima et al[19] | M | 47 | 1b | IFNα-2a + RBV | 8 wk | Incomplete response |
| Medeiros et al[20] | M | 40 | NR | IFN-α + RBV (for 24 wk) and Peg-IFNα-2a + RBV | 36 wk | CR |
| Dimitroulopoulou et al[21] | F | 20 | 3 | IFNa | 28 wk | CR |
| Sebastiano et al[22] | F | 38 | 4 | Peg-IFNα-2b | 4 wk | CR |
| Fujii et al[23] | F | 24 | NR | IFNa | 4 wk | CR |
| Sagir et al[24] | M | 45 | NR | Peg-IFNα-2b + RBV | 10 wk | CR |
| Pockros et al[25] | M | 61 | 1b | IFNa | 16 wk | CR |
| Jiménez-Sáenz et al[26] | M | 46 | NR | IFNα-2b | 144 wk | CR |
| Tappero et al[27] | F | NR | IFNα-2a | 8 wk | CR |
| Dourakis et al[28] | M | 39 | NR | IFNa | 32 wk | CR |
| Dourakis et al[29] | F | 64 | NR | IFNa | 24 wk | CR |
| Shrestha et al[30] | M | 41 | NR | IFNa | NR | CR |
| Demirturk et al[31] | NR | NR | NR | Peg-IFNα + RBV | NR | CR |

CR: Completely resolved; NR: Not reported; HCV: Hepatitis C virus; IFN: Interferon; Peg-IFN: Pegylated-IFN; AITP: Autoimmune thrombocytopenia; RBV: Ribavirin; iv: Intravenous.

effect is observed in course of interferon treatment. Thrombocytopenia is usually defined as a platelet count less than 100000/microL. Severe thrombocytopenia (< 50000/microL) is associated with increased bleeding risk during invasive procedures, while spontaneous and even severe bleeding could be observed in patients with platelet count less than 1000/microL.

Thrombocytopenia is a frequently observed in patients with haematological disorders, with HCV infection, with hypersplenism associated to liver cirrhosis or related to drug assumption. Drug-induced thrombocytopenia develop through two main mechanisms: (1) bone marrow toxicity (i.e., cytotoxic drugs) resulting in reduced production of all blood cells (red cells, white cells and platelets); and (2) increased destruction of normal platelets (both immune-mediated or not)[28]. The incidence of drug induced AITP in the general population is approximately 10 cases per million inhabitants per year; and its pathogenesis is not completely understood yet; however, IgG-type antibodies against platelet glycoprotein (GP) IIb/IIIa, GP Ia/IIa, and/or GP I b/IX seem to play an important role[29].

In literature, we found several cases of PegIFN-induced autoimmune cytopenias; among those, severe life-threatening AITP, although rare, is a well-documented and recognized adverse event.

To our knowledge, 24 cases of AITP are related to interferon-based treatment for HCV; among those, only one occurred after treatment discontinuation[16] (Table 1).

In the reported case, the patient experienced an episode of severe thrombocytopenia three weeks after antiviral therapy completion, despite negative HCV-RNA (the patient achieved a sustained virological response): the concomitant presence of spontaneous bleeding, anti-platelets antibodies positivity, the exclusion of all other possible causes (i.e., viral and Helicobacter pylori infection, haematological or autoimmune disorders and other concomitant therapies) led to the diagnosis of Peg-IFN-induced AITP.

The relationship between AITP and discontinuation of the drug, in our case, could be explained by the long half-life of Peg-IFNα-2a (T1/2 = approximately 160 h); since five plasma half-lives are necessary to eliminate about 99% of administered drug, 33 d are necessary for a 99% clearance of Peg-IFNα-2a[30].

Peg-IFN-induced autoimmune diseases may appear even after treatment withdrawal; however, we encourage the investigation all other causes of autoimmunity, especially when a tight time-correlation with the event is absent.

Based on the latest guidelines on the management of AITP[31], we prescribed a first-line long course of corticosteroids (e.g., prednisone 1 mg/kg orally for 21 d then tapered off); in this case, the patient presented a rapid improvement in platelet count after first-line treatment (Figure 1); therefore the administration of
IV immunoglobulin was not necessary. In fact, immunoglobulin infusion should be prescribed, together with corticosteroids, when a rapid increase in platelet count is clinically required\(^\text{[30]}\). In non-responsive cases, rituximab may be an option. Plateletus infusion should be considered only in cases of severe thrombocytopenia associated with active bleeding. In cases of AITP survival time of infused platelets is reduced to a few hours. However, this practice can help to control acute bleeding\(^\text{[30]}\).

Literature review shows a higher incidence of AITP in patients treated with Peg-IFN-α-2b compared to those treated with α-2a; however, published data are insufficient to assume a greater immunogenicity of Peg-IFN-α-2b over Peg-IFN-α-2a\(^\text{[30]}\).

In conclusion, physicians prescribing pegylated interferon should be aware that acute AITP can occur both during and after treatment. Consequently, it seems logical to us that anti-platelet antibodies dosage should be determined in all patients presenting with thrombocytopenia both during treatment and after discontinuation. A deep knowledge and prompt recognition of interferon-related adverse events is even more important with the availability of interferon-sparing treatment regimens.

**COMMENTS**

**Clinical diagnosis**
Gingival spontaneous bleeding was the first finding in this patient; severe thrombocytopenia coupled with positive anti-platelet antibodies led to the diagnosis.

**Differential diagnosis**
All other causes of autoimmune thrombocytopenia (AITP) had been evaluated; moreover, the not-tight-time-correlation required an accurate evaluation of possible hematological or autoimmune disorders, assumption of concomitant drugs.

**Laboratory diagnosis**
Severe thrombocytopenia (1000/mm\(^3\)) and positive anti-platelet antibodies suggested the diagnosis of AITP.

**Treatment**
Treatment with intravenous corticosteroids led to prompt total platelet count increase within one week; after 8 wk of treatment, normal platelet count and negative anti-platelet antibodies were observed.

**Related reports**
All related cases of interferon-related AITP were reviewed and summarized in

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