



## UNUSUAL RESPONSE TO ELTROMBOPAG AND DOSE ADJUSTMENT IN PATIENT WITH A DIAGNOSIS OF REFRACTORY IMMUNE THROMBOCYTOPENIA

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<p><b>Article Info</b>  <i>Received 06/01/2016</i>  <i>Revised 27/01/2016</i>  <i>Accepted 05/02/2016</i></p> <p><b>Key words:</b>          Thrombocytopenia,          Thrombopoietin          receptor,          Eltrombopag.</p>	<p><b>ABSTRACT</b>          Immune thrombocytopenia (ITP) is an acquired autoimmune disease with isolated thrombocytopenia in which myeloid and erythroid series not affected. Refractory ITP is a term used in ITP patients with thrombocytopenia despite corticosteroid therapy and splenectomy. Treatment in refractory ITP is initiated depending on the grade of thrombocytopenia and in presence of bleeding and clinical conditions requiring therapy. Most commonly used agent in this patient group is eltrombopag which is a thrombopoietin (TPO) mimetic. Based on these information, we report a case from our clinic with unusual response to eltrombopag and subsequent dose adjustment for this response; since there no drug use matching this dose adjustment in the literature.</p>
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### INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired autoimmune disease with isolated thrombocytopenia in which myeloid and erythroid series not affected [1]. It is known that autoantibodies against platelets develop secondary to B cell dysfunction against GPIIb/IIIa and GPIb/IX which are glycoproteins on the surface of platelets [2]. Thrombocytopenia occurs with autoantibody-mediated destruction of platelets in spleen by macrophages as well as megakaryocytic damage in bone marrow due to autoantibodies and/or cytotoxic T cells [3, 4]. Chronic ITP is defined as persistence of ITP for 12 months or more. Refractory ITP is a term used in ITP patients with thrombocytopenia despite corticosteroid therapy and splenectomy [5]. Treatment in refractory ITP is initiated depending on the grade of thrombocytopenia and in presence of bleeding (mainly purpuric skin lesions, mucosal bleeding; rarely, internal organ bleeding and life threatening bleeding) and clinical conditions requiring therapy (advanced age, history of bleeding, active gastrointestinal problems, need for anticoagulant use,

additional disorders interfering with hemostasis, head trauma, surgical interventions, parturition etc). The aim of therapy is not to bring platelet count to normal range but to preserve it at a level sufficient to control major bleeding risk. After splenectomy in about 20% of patients platelet count and effectiveness may not be sufficient to control bleeding. In this patient group, among various treatment options combination therapies may be tried. This group mainly includes agents like TPO mimetics, rituximab, cyclophosphamide, cyclosporine, vinka alkaloids, azathioprine etc. [6]. Eltrombopag which is a TPO mimetic interacts with transmembrane region of TPO-receptor and induces proliferation via signal pathways similar to but not identical with endogenous TPO and megakaryopoiesis differentiation from bone marrow progenitor cells [7]. Starting dose of eltrombopag in ITP is 50 mg/day. Studies on drug pharmacokinetics have shown that plasma level is higher in human with East Asian origin independent from body weight. Thus, starting dose is 25 mg/day for these people. Eltrombopag is a treatment option requiring close



monitorization of platelet count and dose adjustment according to platelet count [8,9]. In this article, we report a case from our clinic with exaggerated response to eltrombopag treatment and subsequent dose adjustment for this response; since, there is no drug use matching this dose adjustment in the literature.

### Case

A 33 years old male patient presented with petechiae in 1995 has been started 1 mg/kg/day methyl prednisolone treatment with a diagnosis of immune thrombocytopenia after detecting thrombocytopenia. Platelet count was restored to normal after treatment and the dose was tapered and then treatment was completely stopped. Two months later platelet count has decreased again and after restoration of platelet count by methylprednisolone therapy, splenectomy was performed. The patient was followed up between 1995-2007 while in remission and the patient referred to hospital because of petechiae in 2007 without any other complaint. Platelet count was 12.000/mm<sup>3</sup> in CBC and thus bone marrow aspiration was done. Bone marrow aspiration has showed increase in megakaryocytes but no associated infiltration or dysplasia. Accessory spleen was seen in spleen scintigraphy and splenectomy was repeated. The patient was in remission after splenectomy for 2 years until his referral due to petechiae and nose bleeding and platelet count was found as 10.000/mm<sup>3</sup> at this time. After screening for accessory spleen steroid therapy was repeated. Avascular necrosis of femoral head was detected in radiological imaging because of pain in the hip joint in the second month of steroid therapy. Thus, the steroid therapy was stopped and respectively cyclosporine 3 mg/kg/day, vincristine 2 mg once weekly for 4 weeks, rituximab 375 mg/m<sup>2</sup> once weekly for 4 weeks were given but there was no response. Then, eltrombopag was started. Platelet count was over 250.000/mm<sup>3</sup> by eltrombopag 50 mg/day but by 25 mg adequate response wasn't obtained, and thus eltrombopag 50 mg was given in every other day. Since platelet count was over 250.000/mm<sup>3</sup>, under close monitorization of hemogram values eltrombopag treatment was given respectively as 50 mg once in every 3 days and at last once in every 4 days. When eltrombopag 50 mg was given once in every 4 days platelet count was between 100.000-250.000/mm<sup>3</sup> and there was no bleeding. The patient has been taking eltrombopag 50 mg once in every 4 days for the last fifteen months and platelet count is between 100.000-250.000/mm<sup>3</sup> and there is no bleeding.

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### DISCUSSION AND CONCLUSION

Chronic ITP is defined as persistence of ITP for 12 months of more; whereas refractory ITP is a term used in ITP patients with thrombocytopenia despite corticosteroid therapy and splenectomy [5]. Treatment in refractory ITP is initiated depending on the grade of thrombocytopenia and in presence of bleeding and clinical conditions requiring therapy. TPO-R agonist use in refractory ITP patients is being widely accepted. Romiplostim and eltrombopag is two current agents within this group [10]. Eltrombopag interacts with transmembrane region of TPO-R and induces signalization cascades via signal pathways similar to but not identical with endogenous TPO and induces megakaryopoiesis differentiation from bone marrow progenitor cells [7]. Eltrombopag binds to plasma protein and at a high rate to albumin (>99.9%) in human after absorption [11,12]. Starting dose of eltrombopag in ITP is 50 mg/day. Dose modification which is out of routine use of the drug may be related to absorption concentration of the drug or interaction of the drug at the receptor level. In addition, studies on drug pharmacokinetics have shown there are differences especially in East Asian populations. Because of this difference the drug dose used in this population is lower [13]. Recent studies have shown that genetic polymorphism may have some effects on treatment response [14, 15]. Dose adjustment in our patient was based on the clinical condition and platelet count of the patient and differed from the information in summary of product characteristics.

In conclusion, in order to clarify the questions regarding this case, drug plasma concentration should be measured pharmacologically, TPO-R should be assessed, genetic polymorphism should be investigated or ethnic origin of the patient should be sought by the help of a pedigree.

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### CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

### STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.



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