

Review article:

THE ROLE OF ELTROMBOPAG AND ROMIPLOSTIM AS THE THROMBOPOIETIN RECEPTOR AGONIST (TPO-RA) IN TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP): WHAT IS TPO-RA, WHEN TPO-RA IS USED AND HOW TO TAKE TPO-RA?

Jefri Pratama Susanto

Brawijaya University, Faculty of Medicine, Malang, Indonesia

ABSTRAK

Idiopathic Thrombocytopenic Purpura (ITP) merupakan penyakit autoimun yang ditandai dengan trombositopenia akibat destruksi trombosit yang berlebihan. Namun pada beberapa kasus didapatkan baik destruksi trombosit dan penurunan kadar trombopoietin. Oleh karena itu muncul paradigma baru dalam penatalaksanaan ITP yaitu dengan meningkatkan kadar trombopoietin dengan menggunakan eltrombopag atau romiplostim sebagai agonis reseptor trombopoietin. Eltrombopag diberikan secara per oral sedangkan romiplostim diberikan secara subkutan atau intravena dan dosis kedua obat disesuaikan berdasarkan jumlah hitung trombosit. Baik eltrombopag dan romiplostim dapat digunakan pada kasus ITP yang memberikan respon minimal terhadap glukokortikoid, immunoglobulin intravena ataupun splenektomi. (FMI 2015;51:203-207)

Kata Kunci: Agonis reseptor trombopoietin, eltrombopag, ITP, Romiplostim, trombopoietin.

ABSTRACT

Idiopathic thrombocytopenic purpura is a autoimmune disease characterized thrombocytopenia casued by excessive platelet destruction. However, both platelet destruction and reduced thrombopoietin level are occurred in some cases. Therefore, new management of ITP is emerged which target is to increase platelet production rate via eltrombopag or romiplostim as the thrombopoietin receptor agonist (TPO-RA). Eltrombopag is given orally while romiplostim is given subcutaneously or intravenously and dose adjustment is depend on platelet count. Both eltrombopag and romiplostim is indicated in minimal response glucocorticoid or intravenous immunoglobulin or splenotomy treatment. (FMI 2015;51:203-207)

Keywords: Thrombopoietin receptor agonist (TPO-RA), thrombopoietin, eltrombopag, ITP, romiplostim.

Correspondence: Jefri Pratama Susanto, Faculty of Medicine, Brawijaya University, Malang, Indonesia. Phone: 08123043514/087859298055. Email: j3ff_12y@yahoo.com

INTRODUCTION

Idiopathic Thrombocytopenic Purpura (ITP) is an autoimmune disease characterized by transient or persistent thrombocytopenia ($<100 \times 10^9/L$). The term “newly diagnosed ITP” is used to explain all ITP cases, which are just diagnosed. Persistent ITP is defined as ITP lasting from 3 to 12 months since the first diagnosis, and chronic ITP is defined as ITP lasting more than 12 months. Secondary ITP includes all immune mediated thrombocytopenia except primary ITP (Cheng, 2012).

For many years, the pathophysiology of ITP is caused by excessive platelet destruction and clearance and this is auto reactive antibody mediated process against platelet glycoprotein. Even though platelet life span often reduced dramatically, in several patients, this platelet life span is slightly reduced and platelet production rate is suboptimal. Overall, platelet production rate is decreased in 40% patient of ITP.

Based on this findings, autoantibody against platelet glycoprotein is found to disturb megakaryocytes maturation, resulting in decreased platelet production. More over, most megakaryocytes shows ultra structural features of apoptosis or para-apoptosis and this morphological changes can be proven in culture megakaryocytes with ITP plasma. In vitro study, antibody that attack platelet glycoprotein (GP) Ib-IX-V might cause thrombocytopenia via megakaryopoiesis inhibition and pro-thrombocytes formation. (Stasi et al, 2011).

Most ITP treatments are aimed to reduce autoantibody production and or to slow down opsonized platelet, which in the end will be engulfed by macrophage. Based on the pathophysiology mentioned above, some of patients of ITP have platelet production disturbance rather than excessive platelet destruction (Stasi et al, 2011). Therefore, this review article will discuss about ITP management focus on thrombopoietin receptor agonist (TPO-R) which are eltrombopag and romi-

plolistim, what are they, when they are used and how to take these drugs.

THROMBOPOIETIN RECEPTOR AGONIST (TPO-R)

Thrombopoietin is a humoral regulator of platelet production. Endogenous thrombopoietin is produced mainly in liver, bind specifically and activates thrombopoietin receptor, which is located on megakaryocytes membrane and induces cytoplasmic signaling to produce platelet (Imbach and Crowther, 2011).

Fact has shown that thrombopoietin level in ITP is low and it is not well compensated by the body, resulting in new concept of ITP management by stimulating thrombopoietin receptor exogenously. First trial is by using recombinant thrombopoietin, but this trial is stopped due autoantibody associated thrombocytopenia against endogenous thrombopoietin (Imbach and Crowther, 2011). There fore, the development of second generation of thrombopoietin receptor agonist is started. Structurally, this second generation of TPO-R is different with thrombopoietin, so there will be no autoantibody formed. Romiplostim is a syntethic fusion protein with four peptides consist of 14 amino acid residue connected to an IgG fragment Fc, this bond form a "peptibody" (Figure 1A) (Imbach and Crowther, 2011). Romiplostim binds to thrombopoietin receptor and activates intercellular signaling pathway (JAK_STAT pathway and MAP kinase), where this pathway will stimulate platelet production (Figure 1C). Eltrombopag is a small non-peptide molecule bound to trans membrane of thrombopoietin receptor and then activates the same intercellular pathway as activated by romiplostim (Figure 1B and Figure 1C) (Imbach and Crowther, 2011).

ELTROMBOPAG

Eltrombopag is a non-peptide thrombopoietin receptor agonist which is administered orally in tablet. In a pre-clinic study, eltrombopag stimulates megakaryocytes differentiation and proliferation by stimulation in thrombopoietin receptor and this drug is dose-dependant (Stasi et al, 2011). Mechanism action of eltrombopag to activate thrombopoietin receptor is different with romiplastim. Eltrombopag interacts with the thrombopoietin receptor at a binding site distant from that of thrombopoietin and appears to initiate signal transduction by a mechanism different from that of endogenous thrombopoietin. There fore, eltrombopag and endogenous thrombopoietin will not bind at the same

site, so competitive bind will not happen, in fact these can give synergistic effect (Stasi et al, 2011).

Recommendation for eltrombopag initial dose to most patients is 50mg/day and given orally. Dose adjustment is based on platelet count (maximal dose is 75mg/day or minimal dose 25mg/day). This dose adjustment can be seen in table 1 (Ashariati, Sedana, Bintoro and Diansyah, 2014). Patient with hepatic dysfunction and Asians should start the drug with 25mg/day. Eltrombopag should be taken 1-2 hours after meals due to its interaction with food. Tis drug should not be taken within 4 hours after taking antacid (Imbach and Crowther, 2011). Increase in platelet count can be sustained after 8 days using the drug and then decrease after 12 days discontinuation of the drug. Half time of the drug is approximately 12 hours (Siegal et al, 2013).

ROMIPLOSTIM

Romiplostim is a recombinant protein also known as the "peptibody". Romiplostim bind and activates thrombopoietin receptor through a similar mechanism as endogenous thrombopoietin via signaling pathway activation such as tyrosine phosphorylation janus kinase 2 and signal transducer and activator of transcription 5 (STAT). Romiplostim increase megakaryocytes maturation in vitro and it is a competitive agonist with thrombopoietin to bind with human thrombopoietin receptor in vitro (Stasi et al, 2011). Romiplastim can be given intravenously or subcutaneously. The platelet count escalation can be achieved within 5-8 days and then back to baseline on 28 days (SIEGAL et al, 2013).

Recommendation initial dose of romiplostim is 11 ug/kgBB given subcutaneously, once a week with dose adjustment based on platelet count. This dose adjustment can be seen in table 2 (Bussel et al, 2009). The therapeutic dose is approximately 3-4 ?g/kgBB with maximal dose is 10 ?g/kgBB. Romiplostim is available in 250-?g and 500-?g vials as a lyophilized powder.

THROMBOPOIETIN RECEPTOR AGONIST INDICATION

The goal of ITP management is to maintain platelet count in which can minimize the bleeding tendency. Observation alone is should be done when no bleeding or mild bleeding occurs while thrombocyte count is $30 \times 10^9/L$ in adult. Management in patient with low platelet count is indicated if only active bleeding happens or platelet count is very low ($<10 \times 10^9/L$).

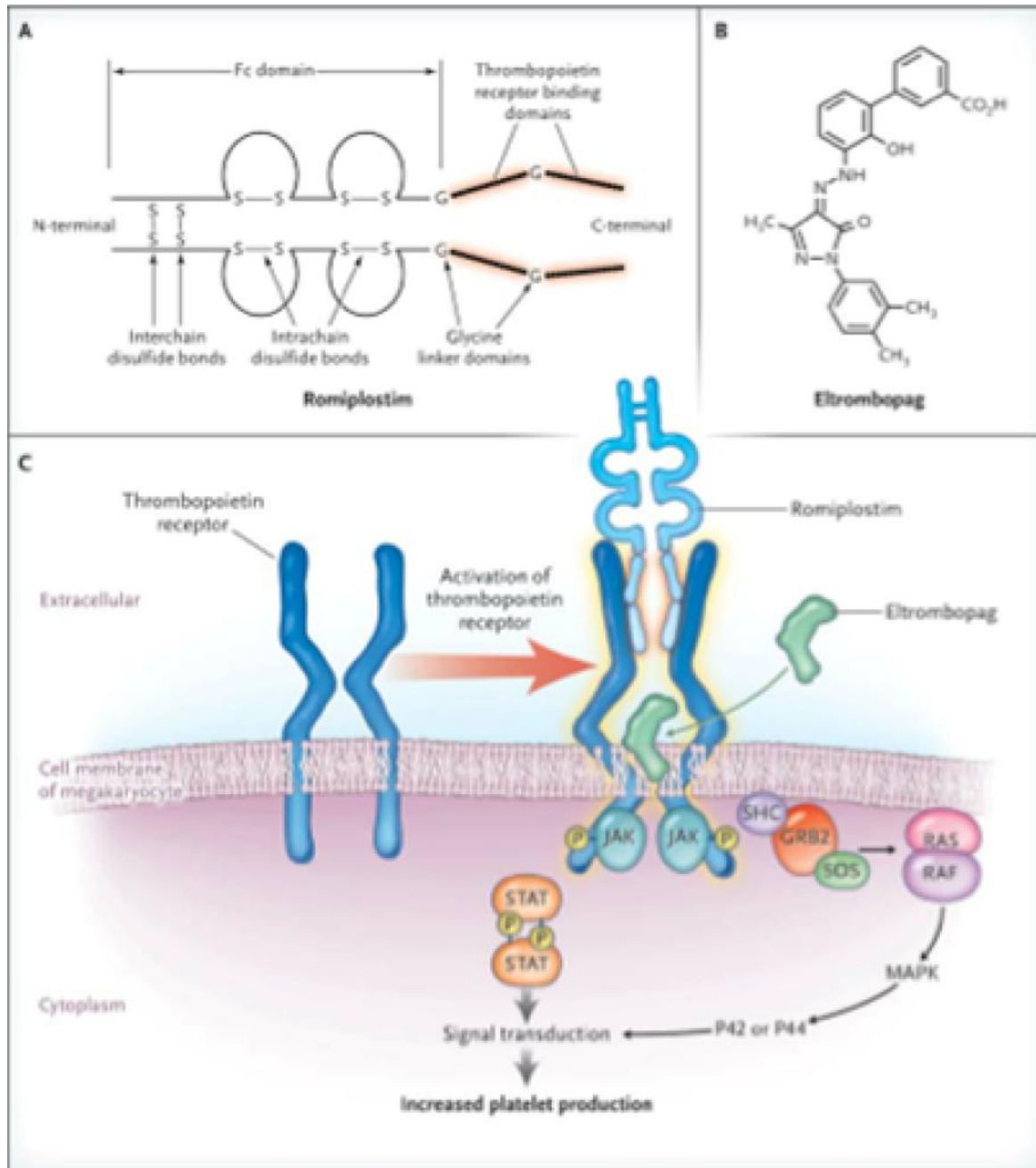


Figure 1. Romiplostim and Eltrombopag Structure and Its Intercellular Pathway. Panel A shows chemical structure of romiplostim. Panel B shows chemical structure of Eltrombopag. Panel C shows mechanism action of Romiplostim and Eltrombopag. GRB2 denotes growth factor receptor-binding protein 2, JAK Janus kinase, MAPK mitogen-activated protein kinase, P phosphorylation, RAF rapidly accelerated fibrosarcoma kinase, RAS rat sarcoma GTPase, SHC Src homology collagen protein, and STAT signal transducer and activator of transcription (Imbach and Crowther, 2011)

Table 1. Eltrombopag dose adjustment (Ashariati, Sedana, Bintoro and Diansyah, 2014).

Platelet Count	Dose Adjustment and Response
<50x10 ⁹ /L after taking eltrombopag for minimal 2 weeks	Increase daily dose by 25 mg to a maximum of 75 mg daily. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
200-400x10 ⁹ /L at anytime	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of any dose adjustments.
>400x10 ⁹ /L	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is less than 150x 10 ⁹ /L, reinstate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinstate therapy at 12.5 mg daily.
>400x10 ⁹ /L after 2 weeks with minimal dose	Permanently discontinue eltrombopag.

Table 2. Romiplostim Dose Adjustment (Bussel et al, 2009)

Platelet Count	Dose Adjustment and Response
≤10 x10 ⁹ /L	Dose increased by 2 µg/kgBB every week when platelet counts were ≤10 x10 ⁹ /L (Dose could be increased every week.)
10-50 x10 ⁹ /L	Dose increased by 2 µg/kgBB after 2 consecutive weeks of platelet counts <50 x10 ⁹ /L. (Dose could be increased every 2 weeks.)
50-250 x10 ⁹ /L	Dose could be adjusted by 1 µg/kgBB (increased or decreased) at the investigator's discretion, no more frequently than every 2 weeks. The maximum dose was 10 µg/kgBB weekly.
250-400 x10 ⁹ /L	Dose reduced by 1 µg/kgBB after 2 consecutive weeks of platelet counts in this range. (Dose could be reduced every 2 weeks.)
≥400 x10 ⁹ /L	Next scheduled dose was held. On the next scheduled dosing day that the platelet count was < 250 x10 ⁹ /L, the dose was reduced by 1 µg/kgBB

First line treatment of ITP generally is glucocorticoid, intravenous immunoglobulin or both. The only second line treatment that can sustain platelet count escalation is splenectomy. Rituximab is used widely as the second line treatment, even though the mean duration of response is 10,5 months. Romiplostim and eltrombopag have been approved by the FDA for chronic ITP with minimal response to glucocorticoid, intravenous im-

munoglobulin or splenectomy. Clinically, both romiplostim or eltrombopag is used in chronic or persistent ITP and ongoing bleeding with or without previous splenectomy and one or more courses of rituximab. Since this thrombopoietin receptor agonist pass through placenta, so the uses of this drug in pregnancy is prohibited (Imbach and Crowther, 2011)

CONCLUSION

The new paradigm of ITP pathophysiology, which is reduced thrombopoietin level, has opened a new perspective to the dramatic advance of ITP management. Eltrombopag acts through a different pathway as endogenous thrombopoietin while romiplostim acts the same as endogenous thrombopoietin. Eltrombopag is administered orally and can be started with 25mg/day. Romiplostim is administered sub-cutaneously or intravenously and the starting dose is 2 ug/kgBB every week. Both eltrombopag and romiplostim as the thrombopoietin receptor agonist (TPO-RA) can be used in chronic ITP with minimal response to first or second line treatment of ITP.

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