

# Thrombopoietin Receptor Agonists for Treatment Thrombocytopenia in Dengue Fever

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**Abstract:** *Dengue fever is considered to be the most prevalent mosquito - borne viral disease worldwide and has proven to be life - threatening at times. Thrombocytopenia occurs in mild and severe cases of dengue fever. commonly observed. Severe thrombocytopenia and bleeding episodes with platelet counts well below the normal range are considered fatal consequences of dengue fever requiring appropriate and timely treatment. Thrombopoietin receptor agonists (TPO - RA) play an important role in stimulation thrombus formation. However, traditional meta - analyses have shown conflicting results efficacy of thrombopoietin receptor agonists and placebo. This review is based solely on hypotheses and articles showing a positive response to thrombopoietin receptor agonists (TPO - RA) in dengue fever after web - based searches on various search engines. Furthermore, this review highlights the need for high - quality randomized trials and meta - analyses to demonstrate the safety and efficacy of thrombopoietin receptor agonist (TPO - RA) therapy in patients with dengue - associated thrombocytopenia.*

**Keywords:** thrombopoietin receptor agonist; dengue fever; inpatient; viral disease; thrombocytopenia

## 1. Introduction

Dengue is a viral disease that is rampant in tropical and subtropical areas of the world. It is caused by 4 antigenically distinct dengue virus (DENV) serotypes DENV1, DENV2, DENV3 and DENV4, of the genus Flavivirus. The infection is transmitted between humans by Aedes mosquito and man is the main reservoir of the virus. The clinical feature ranges from self limiting Dengue fever (DF) to Dengue Haemorrhagic Fever (DHF). DHF is characterized by severe thrombocytopenia and haemorrhagic manifestations which can be associated with circulatory collapse and shock. As per recent WHO classification scheme for dengue, patients are classified into two groups “dengue” and “severe dengue” (1).

## Epidemiology

Dengue is widespread throughout the tropics, with risk factors influenced by local spatial variations of rainfall, temperature, relative humidity, degree of urbanization and quality of vector control services in urban areas. (2)

In 2017, a significant reduction was reported in the number of dengue cases in the Americas - from 2 177 171 cases in 2016 to 584 263 cases in 2017. This represents a reduction of 73%. Panama, Peru and Aruba were the only countries that registered an increase in cases during 2017. Similarly, a 53% reduction in severe dengue cases was also recorded during 2017. (2)

After a drop in the number of cases in 2017 - 18, sharp increase in cases is being observed in 2019. In the Western Pacific region, increase in cases have been observed in Australia, Cambodia, China, Lao PDR, Malaysia, Philippines, Singapore, Vietnam while Den - 2 was reported in New Caledonia and Den - 1 in French Polynesia. Dengue outbreaks have also been reported in Congo, Côte d'Ivoire, Tanzania in the African region; Several countries of the American region has also observed an increase in the number of cases. An estimated 500 000 people with severe

dengue require hospitalization each year, and with an estimated 2.5% casefatality, annually. However, many countries have reduced the case fatality rate to less than 1% and globally, 28% decline in case fatality have been recorded between 2010 and 2016 with significant improvement in case management through capacity building at country level (2).

## Mechanism Thrombopoietin Receptor Agonists for Treatment of Thrombocytopenia in Dengue Patient

Thrombocytopenia in dengue fever is caused by peripheral destruction and addition of bone marrow to varying degrees. Platelet decrease is indicated by the platelet index and the role of the bone marrow that causes thrombocytopenia in patients with dengue fever. Research shows that most of the platelet averages of dengue patients show platelet damage.

The platelet index causes platelet destruction and prevents thrombocytopenia. In rest of the patients, hematological parameters suggest decreased production which could account for thrombocytopenia (3). Thrombocytopenia, associated with an increased risk of bleeding and life - threatening hemorrhage, is considered as a potential indicator of clinical severity in dengue patients. It reduces the quality of life of the patients. The degree of thrombocytopenia varies in dengue infections, with platelet counts in some patients becoming dangerously low:

<10, 000 but bleeding yet to occur or platelets <50, 000 with bleeding manifestations. In 2008, the United States Food and Drug Administration (USFDA) approved two TPO - R agonists: eltrombopag and romiplostim for the treatment of idiopathic thrombocytopenic purpura (ITP) and other thrombocytopenic conditions. (4)

In the last decade, an improved understanding of thrombopoiesis and the function of its key regulator, thrombopoietin (TPO), led to the development of targeted agents called TPO receptor agonists (RAs), which are able to stimulate megakaryopoiesis, thus increasing platelet production. (5)

Hence, the TPO level is inversely proportional to platelet production and platelet mass. To treat thrombocytopenia, recombinant TPO (rTPO) was used initially to enhance the production of platelets in patients. An effective treatment strategy involves the utilization of TPO receptor (TPO - R) agonists, which mimic the mechanism of action of endogenous TPO on its receptors and induce the activation, proliferation, and maturation of megakaryocytes and thereby enhance platelet production. (4)

### Thrombopoietin receptor agonists in clinical use: eltrombopag and romiplostim

Eltrombopag is an oral, small - molecule, nonpeptide TPO - RA. Similar to endogenous TPO, eltrombopag binds TPOR and activates the JAK2/STAT signalling cascade, which leads to increased platelet production. Eltrombopag shows no structural or sequence homology to endogenous TPO, which eliminates any risk of cross - reactive antibody development. Furthermore, unlike endogenous TPO, eltrombopag binds the transmembrane domain of TPOR and thus does not compete with TPO for receptor binding. As a result, eltrombopag may enhance endogenous TPO function rather than substitute for it, as suggested by in vitro studies the European Union and USA, eltrombopag is approved for treatment of adult and paediatric patients (aged  $\geq 1$  year) with chronic ITP (cITP) who had an insufficient response to corticosteroids, immunoglobulins (Ig), or splenectomy; adults with severe aplastic anaemia (SAA) with an insufficient response to first - line therapy and not eligible to have bone marrow transplantation; and thrombocytopenia in patients with chronic hepatitis C virus infection to allow the initiation and maintenance of interferon - based therapy (5)

Eltrombopag is taken orally once daily on an empty stomach (i. e. 1 h before or 2 h after meals). Because eltrombopag can bind to divalent ions, resulting in reduced drug absorption, it should not be taken 2 h before or 4 h after a calcium - rich meal or ingestion of supplements that contain divalent ions.

Eltrombopag is well tolerated and safe for long - term use. The most common drug - related adverse events (AEs) in cITP registration studies were gastrointestinal or infection related. Romiplostim is a recombinant fusion protein (peptibody) that binds and activates TPOR. Romiplostim and endogenous TPO have the same TPOR binding site, suggesting a common mechanism of action. Romiplostim is a homodimer of a single - chain peptide consisting of the human Ig G1 (IgG1) Fc region linked to a TPOR binding domain. In the European Union and USA, romiplostim is approved for treatment of adults with cITP with an insufficient response to first - line treatments. Romiplostim is administered via weekly subcutaneous injections in a clinic by a healthcare provider during treatment optimisation (5)

## 2. Discussion

Dengue fever is an epidemic that attacks more than 100 countries. Not only causes death but also material losses. Therefore a method of coping is made based on the factors of its spread and treatment of DHF patients.

One of the clinical manifestations of DHF is thrombocytopenia.

Thrombocytopenia can be experienced by children and adults and will cause sufferers more susceptible to bleeding. Although rare, untreated thrombocytopenia can lead to internal bleeding that can even be fatal (eg brain bleeding). Especially if the patient's platelet count is below 10, 000 per microliter of blood. for people with severe thrombocytopenia, the treatment method they will undergo depends on two things, namely the cause and severity of the condition. Recommended treatment for thrombocytopenia is platelet transfusion and proper fluid replacement.

Efforts around the world have been made to develop new management strategies to fight these fatal complications in patients with dengue fever. The main treatment goal for severe thrombocytopenia patients is to stabilize platelet counts to prevent bleeding.

At present there is only one single study that reports that romiplostim can overcome thrombocytopenia in patients with dengue fever. This finding is related to previous findings about the effectiveness of TPO - R agonists in ITP patients, so this suggests the need to consider TPO - R as a treatment for severe thrombocytopenia due to dengue fever. To achieve this, high - quality comparative clinical data is needed to analyze the relative efficacy, safety, side effects, and cost effectiveness of romiplostim and eltrombopag in the treatment of dengue fever, as well as their impact on the quality of life of patients. Deep insight into the importance of this molecule in the treatment of DHF patients with thrombocytopenia is very important. Most importantly, it never hurts to try this TPO - R agonist in the management of thrombocytopenia, because this simple step, if truly successful, can save millions of patients with critical dengue fever.

## References

- [1] Charaniya R, Ghosh A, Sahoo R. Intravenous Immunoglobulin Responsive Persistent Thrombocytopenia after Dengue Haemorrhagic Fever.2016; 10 (4): 10–1.
- [2] World Health Organization Western Pacific Region. Dengue Situation Update Number 564 : Update on the Dengue situation in the Western Pacific Region.2017; (564): 1–5. Available from:
- [3] [http://www.wpro.who.int/emerging\\_diseases/dengue\\_biweekly\\_20170117.pdf?ua=1](http://www.wpro.who.int/emerging_diseases/dengue_biweekly_20170117.pdf?ua=1)
- [4] Krishnamurthy V, Rajeshakar R, Doreswamy SM. Thrombocytopenia in Dengue Illness : Destruction, Suppression and Composite Platelet Index : A Retrospective Study. Ann Pathol Lab Med.2016; 3 (5): 465–70.
- [5] Roy S. Thrombopoietin Receptor Agonists : Can These Be the Future Answer to the Deadly Thrombocytopenia in Dengue Fever ? 2019; 11 (4): 1–12.
- [6] Rodeghiero F, Carli G. Beyond immune thrombocytopenia: the evolving role of thrombopoietin receptor agonists. Ann Hematol.2017; 96 (9): 1421–34.