A Report on Comparative Safety and Efficacy of Eltrombopag in the treatment of Thrombocytopenia

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Introduction

Thrombocytopenia is defined as a platelet count below 150 × 10^9/L, the 2.5th lower percentile of the normal platelet count distribution. Typically, platelet counts higher than 50 × 10^9/L do not lead to clinical problems unless platelet dysfunction coexists with the low count; rather, they are picked up on a routine complete blood count. Medical help is usually sought by a patient with platelet counts less than 30 × 10^9/L, suffering from spontaneous bruising and purpura or with continuous/relatively long-lasting bleeding from injuries/wounds. Clinically significant spontaneous bleeding does not usually occur until the platelet count is less than 10 × 10^9/L[1, 2].

There are numerous causes for thrombocytopenia, defined as a platelet count below 150 × 10 ^{9}/L, and they could be broadly classified as congenital and acquired. Acquired thrombocytopenia could be immune or non-immune. Thrombocytopenia could be a result of decreased marrow production, increased destruction or sequestration/consumption in the periphery, or a combination of decreased production and sequestration. Initial steps in the evaluation of thrombocytopenia include review of the peripheral blood smear to exclude pseudo-thrombocytopenia due to platelet clumping. The peripheral blood smear may also provide clues toward other causes of thrombocytopenia when combined with the complete blood count and a good patient history and physical examination. Thrombocytopenia could be a harbinger of a serious underlying medical condition such as thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT). Therefore, it is always important for the treating physician to evaluate thrombocytopenia in a timely fashion so that the treatment for some of the serious conditions is not delayed[3].

Most patients presenting with immune thrombocytopenia (ITP) either are asymptomatic or have minor muco-cutaneous bleeding. ITP remains a diagnosis of exclusion because there is no reliable diagnostic test to detect

platelet auto antibodies[4]. However, a rapid response to intravenous immunoglobulin (IVIG) or steroids, in addition to being therapeutic, might also aid in the diagnosis of ITP. Platelet auto antibodies or T cell-mediated autoimmunity or both play a role in the pathophysiology of ITP resulting in platelet destruction and reduced platelet production[5]. Although platelet auto antibodies are not used in the diagnosis of ITP, recent work suggests that the lack of platelet-bound antibodies might predict non-responsiveness to Rituximab therapy in patients with ITP[6]. The bleeding phenotype varies significantly in patients with similar platelet counts and may be related to factors such as concomitant medications, age of the patient, and platelet reactivity. There is some evidence to suggest that ITP patients with lower platelet counts and increased platelet reactivity have a lower risk of bleeding[7]. Intracranial hemorrhage is the most dreaded complication of ITP, and history of significant bleeding from other sites predicts for intracranial hemorrhage[8].

Steroids are the mainstay in the first-line treatment of ITP. A two- to four-week course of prednisone (1 mg/kg and taper) or four days of pulsed high-dose (40 mg daily) Dexamethasone given every two to four weeks are the two commonly used steroid regimens[4]. High-dose Dexamethasone was found in one study to be more effective in inducing long-term remission compared with prednisone[9]. Multiple cycles of pulsed Dexamethasone may result in higher long-term remission rates compared with prednisone or a single cycle of Dexamethasone[9, 10]. Two other retrospective studies showed conflicting results when comparing the efficacy of Dexamethasone with that of prednisone[11, 12]. Further prospective studies are needed to conclusively prove the efficacy of one steroid over the other. Given the convenience of a short-course, high-dose Dexamethasone regimen over a longer duration of prednisone, we recommend high-dose Dexamethasone over prednisone for the initial treatment of ITP[13]. Treating physicians should be aware of the fact that a sustained response with high-dose Dexamethasone might require multiple cycles of therapy, although some proportion of the patients might not achieve remission despite this approach. IVIG administered at a dose of 1 g/kg for one or two days is the other first-line treatment option [1]. Given the faster platelet response to IVIG compared with steroids, IVIG is used in conjunction with steroids in patients with severe thrombocytopenia requiring urgent procedures or presenting with moderate to severe bleeding.

Before the advent of thrombopoietin receptor agonists (TPO-RAs), splenectomy and Rituximab were the commonly used second-line agents. A recent single-center cohort study compared 83 splenectomized ITP patients with 83 non-splenectomized ITP patients. Splenectomy resulted in an overall response rate of 52% at 192 months[14]. There was an increase in the venous thromboembolic events and serious infections resulting in hospitalization in the splenectomized population without a decrease in the overall survival. A recent population-matched cohort study demonstrated that splenectomized patients had a 50% overall increased five-year stroke risk compared with the disease-matched cohort (absolute risk 3% versus 2.3%) but that there was no increase in the five-year stroke risk in ITP patients undergoing splenectomy[15]. Another recent large single-center study confirmed the curative nature of splenectomy in more than 50% of the patients undergoing the procedure, and corticosteroid dependence predicted for sustained response after splenectomy[16]. Taking into consideration the high cure rates and the opportunity to avoid long-term medications, we recommend considering splenectomy as the initial second-line treatment option in young steroid-dependent ITP patients. Other common types of Thrombocytopenias include Heparin Induced Thrombocytopenia (HIT), Thrombotic Thrombocytopenic Purpura (TTP) [3].

Rituximab, an anti-CD20 monoclonal antibody, can result in 50 to 60% initial response rates, although only about 20% of the patients maintain the response at five years[17]. A recent randomized control trial comparing Rituximab with placebo demonstrated no difference in the complete remission rates between the two arms at 18 months[18]. Rituximab, when combined with one to three cycles of high-dose Dexamethasone in a first-line setting, could result in higher response rates than Dexamethasone alone[19-21].

Two TPO-RAs, romiplostim and Eltrombopag, were initially used in the third-line setting but have rapidly moved up the ladder to second-line status. These agents have transformed the management for ITP. Long-term follow-up of these agents has demonstrated that they are highly effective and safe in the treatment of patients with ITP[22-24]. TPO-RA could also be used in the first-line setting, in conjunction with steroids and IVIG, to treat severe thrombocytopenia and significant bleeding. There is small proportion of patients who are refractory to one of the agents but may respond to the other[25, 26]. There is also some experience in combining the two agents, given their

different target sites on the thrombopoietin receptor, in patients' refractory to single-agent, second-line therapy[26]. TPO-RA could also be used in combination with other immunosuppressive therapies to improve the response rates in refractory ITP patients[27].

Eltrombopag is an orally bioavailable, small-molecule developed by Novartis and approved by USFDA in 2008 for the treatment of Thrombocytopenia in patients with ITP (Idiopathic Thrombocytopenia) in adults and pediatrics, Thrombocytopenia in patients with Hepatitis C, and treatment of Severe Aplastic Anemia. It is a Thrombopoietin - receptor agonist (TPO-RA) that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells[28].

Pharmacokinetic data[28-31]

Innovator	Novartis (US – 2008)
Brand Name	PROMACTA
Regulatory Approval	USFDA – 2008, CDSCO - 2010
Patent Information (INH-IPM/Orange Book)	US – 20/05/2023, EU – 24/05/2021, JP – 24/05/2026, IND/CN – 24/05/2021, KR – 07/08/2021; ODE – 26/08/2021; ODE (Pediatric) – 26/02/2022
Pregnancy Category	C
Dose & Dosage form	Tablet: 12.5mg, 25mg, 50mg, 75mg, 100mg - OD; Oral suspension: 25mg - OD
ROA	Oral
Approved Indications	Indicated for the treatment of Thrombocytopenia in patients with ITP (Idiopathic Thrombocytopenia) in adults and pediatrics; Thrombocytopenia in patients with Hepatitis C; and Severe Aplastic Anemia
Indications under trial	Phase II: Acute Myeloid Leukaemia; Transplant rejection

Time to peak	2-6 hours
Protein binding	>99%
Metabolism	Hepatic; CYP1A2, CYP2C8, UGT1A1, UGT1A3
Elimination T½	21-32 hours
Excretion	Feces, Urine

Comparison of Safety[28, 32, 33]

Parameter	Eltrombopag	Avatrombopag	Romiplostim
Adverse Effects	URTI – 17%; Nasopharyngitis – 12%; Cough, Diarrhea, Rhinitis, Pyrexia – 9%; Abdominal and Oropharyngeal pain – 8%; Toothache, Rise in ALT – 6%; Rash – 5%; Rise in AST Rhinorrhea – 4%	Pyrexia – 10%; Abdominal pain, Nausea – 7%; Headache – 6%; Fatigue – 4%; Peripheral edema – 3%	Contusion – 41%; URTI – 31%; Oropharyngeal pain – 25%; Pyrexia – 24%; Diarrhea – 20%; Rash – 15%; Purpura, Peripheral Swelling – 7%; Urticaria, Sinusitis, Gastroenteritis – 5%
Black Box Warning	Yes, for inducing Hepatic Decompensation in patients with Hepatitis C	No	No
Precautions	Dosage adjustment is recommended in patients with hepatic impairment in ITP and Severe Aplastic Anemia.	Dosage adjustment is recommended in patients with severe renal impairment	Use with a caution in patients with hepatic and renal impairment

Comparison of Efficacy[28, 32, 33]

Outcome	Eltrombopag	Avatrombopag	Romiplostim
Platelet count response (≥50 x 109 /L) in patients with Chronic Idiopathic Thrombocytopenia	59%-70%	69%	61%
Proportion of subjects not requiring platelet transfusion or any rescue procedure for bleeding	60%	66%	80%
% Patients who achieved target platelet counts and initiated antiviral therapy in Hepatitis C	95%	Not Indicated to treat this condition	Not Indicated to treat this condition
Hematological Response in Severe Aplastic Anemia	40%	Not Indicated to treat this condition	Not Indicated to treat this condition

The pooled proportion of overall response (OR) or complete platelet count response (CR) at 6 months did not vary much between Dexamethasone and prednisone (OR = 54% vs. 43%) (CR = 37% vs. 21%) [34].

Conclusions

- Eltrombopag is an orally bioavailable, small-molecule developed by Novartis and approved by USFDA in 2008 for the treatment of Thrombocytopenia in patients with ITP (Idiopathic Thrombocytopenia) in adults and pediatrics, Thrombocytopenia in patients with Hepatitis C, and Severe Aplastic Anemia. It is a Thrombopoietin-receptor agonist (TPO-RA) that interacts with the transmembrane domain of the human

TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells.

- Steroids (Prednisolone and Dexamethasone) are the mainstay in the first-line treatment of ITP, but their efficacy was found to be no greater than TPO-RAs (Eltrombopag, Avatrombopag and Romiplostim). Further, Steroids are known to cause many adverse events and dependency.
- Unlike Avatrombopag and Romiplostim, Eltrombopag is indicated to treat Idiopathic Thrombocytopenia, Thrombocytopenia in patients with Hepatitis C, and Severe Aplastic Anemia. The efficacy of Eltrombopag in treating ITP was slightly less than that of Romiplostim.
- Safety wise, Eltrombopag carries a black box warning for inducing Hepatic Decompensation in patients with Hepatitis C. A least number of adverse effects were reported by Avatrombopag, while those reported by Romiplostim were on a higher side.
- Looking at the above considerations, it can be eventually concluded that the overall safety vs. efficacy profile of Eltrombopag is favorable. The major advantage being its approval to treat various forms of Thrombocytopenia and Severe Aplastic Anemia.

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