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Eltrombopag – an oral thrombopoietin agonist

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Abstract. – The therapy for immune thrombocytopenic purpura (ITP) has evolved in the recent past. In certain cases therapy for ITP remains inadequate. Thrombopoietin receptor agonists are the latest addition to the armamentarium to manage the thrombocytopenia. While romiplostim was the first second generation thrombopoietin agonist to become available, eltrombopag is particularly attractive as it is an orally bioavailable agent. This review focuses on the use, safety and efficacy of eltrombopag in various clinical conditions.

Key Words:

Thrombopoietin agonists, Eltrombopag, Immune thrombocytopenic purpura.

Introduction

Thrombocytopenia (platelet count <100.000/μL) can accompany a multitude of conditions including disorders of marrow (aplastic anaemia, myelodysplasias, lymphomas and leukemias), enhanced immune mediated platelet destruction (Immune thrombocytopenia, drug induced, secondary to chronic lymphatic leukemia (CLL), etc), disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, septicaemia, hypersplenism, etc. Therapies to treat thrombocytopenia are still evolving and management of threatening thrombocytopenia, in resistant cases, remains inadequate. Thrombopoietin and its receptors are one of the major targets of newer therapies aimed at increasing platelet counts. While first generation thrombopoietin analogues in form of recombinant human thrombopoietin had efficacy in increasing platelet levels initially, development of alloantibodies against these analogues compromised their efficacy on a continued therapy[1].

Second generation thrombopoietin agonists have emerged as a new hope in the management of the thrombocytopenia. The two major thrombopoietin agonists which have a role in the management of the thrombocytopenia, especially the immune thrombocytopenic purpura (ITP), include romiplostim and eltrombopag[2]. Romiplostim is a peptibody administered as once a week subcutaneous injection in non-responding or relapsing ITP. Eltrombopag is a non peptide thrombopoietin agonist which has also been found to be efficacious in similar conditions. The fact that it is orally bioavailable makes eltrombopag a more attractive option.

Chemistry and Structure

Eltrombopag, a non-peptide synthetic thrombopoietin receptor agonist, is a biaryl hydrazone with a molecular weight of 564.6 Dalton.

Mechanism of Action

Thrombopoietin, a cytokine produced in the liver, acts on the thrombopoietin receptors (TPO-R) which are present on the megakaryocytes. Thrombopoietin binds to these receptors and activates the Janus kinase (JAK 2) and tyrosine kinase 2 pathways. This results in the activation of signal transducers and activators of transcription five (STAT 5), phosphoinositide-3 kinase and ras-mitogen activated protein kinase (MAPK)[3-5]. The net result is the differentiation of the bone marrow precursor cells along the megakaryocytic lineage. Thrombopoietin has an antiapoptotic effect and stimulates megakaryocyte maturation. Eltrombopag, in association with metal ions (Zn^{2+}) activates the TPO-R. Since the interaction between eltrombopag and endogenous thrombopoietin on the TPO-R is non-competitive, their effects are additive[6].

Dosage and Administration

The FDA approved eltrombopag in November 2008 for use in immune thrombocytopenic purpura (ITP) patients who had failed at least one prior therapy such as corticosteroids, immunoglobulins or splenectomy. Eltrombopag has been used in

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dose of 25, 30, 50 and 75 mg daily for various durations in trials in patients of chronic ITP. Although the maximum increase in platelet levels is seen with a dose of 75 mg, a dose of 50 mg each day achieves acceptable increase in platelet counts with a fewer side effects[7]. As already mentioned, the drug is taken orally. If the response is inadequate the dosage can be increased to a maximum of 75 mg. One should aim to increase the platelet count to more than 50,000/μL, to prevent bleeding manifestations. However, normalisation of the platelets is not the goal of therapy. The drug is best taken 2 hours prior to or after a meal and 6 hours after the ingestion of antacids, calcium and vitamin supplements to achieve a predictable absorption and attain consistent plasma levels. A randomised control trial conducted by Williams et al[8] indicated that the concomitant administration of eltrombopag with antacids containing magnesium, aluminium or with calcium rich food reduced its bioavailability.

Pharmacokinetics

Around 50% of the drug is absorbed after the oral intake, and peak plasma levels are obtained 2-6 hours after the oral dose. Plasma elimination half-life is 21 to 32 hours. Absorption is interfered by concurrent aluminium and high fat meals, as already mentioned. The drug is highly protein bound. Eltrombopag is extensively metabolized by oxidation via that CYP 1A2 and 2C8 and is then glucuronidated. elimination occurs via both faeces and urine[9].

Indications

As of today eltrombopag is approved by US FDA for use in ITP only. However, emerging data has alluded to the role of this agent in managing thrombocytopenia associated with other etiologies. In patients with hepatitis C related cirrhosis eltrombopag has been shown to increase the platelet counts to above 100.000/μL, thereby, enabling the use of peg-interferon therapy. Use of eltrombopag resulted in a significant number of initially thrombocytopenic patients achieving completion of antiviral therapy[10]. The indications for use of eltrombopag are mentioned in Table I[11].

Immune Thrombocytopenic Purpura (ITP)

A phase 1 placebo controlled trial to assess the safety of various doses (5, 10, 25, 30, 50, 75 mg) given over a period of ten days was conducted in healthy male subjects by Jenkins et al[12]. The study reported no difference in frequency or severity of adverse effects of eltrombopag vis-a-vis placebo. The study also demonstrated thrombopoietic efficacy in normal male subjects. However, lower doses (5, 10 and 20 mg) showed no difference in platelet counts from placebo. Bussel et al[7] studied the effect of eltrombopag in adult patients with chronic ITP who had relapses or were refractory to standard therapy. A dose dependent response in form of increasing platelet counts was seen with the dose of 30, 50 and 75 mg. In 80% of the patients the response was evident within 15 days of initiation of therapy. The safety of this drug was reconfirmed in this trial.

Table I. Indications for use of Eltrombopag.

Approved indication
Immune thrombocytopenic purpura
Under evaluation
Chemotherapy-induced thrombocytopenia.
Hepatitis C related thrombocytopenia
Thrombocytopenia due to marrow abnormalities or hematologic malignancy
Chronic liver disease related thrombocytopenia

Cirrhosis due to Hepatitis C

Chronic hepatitis C virus infection results in autoimmune thrombocytopenia which appears well before the liver failure has set in. Once cirrhosis develops, a decreased production of thrombopoietin from the liver further decreases the platelet count. McHutchinson et al[10] observed a positive effect of eltrombopag on the platelet counts in patients with thrombocytopenia due to HCV related cirrhosis. The increase in platelet counts was helpful in the completion of the antiviral therapy in a significant number of patients. Dose escalation to 75 mg has been shown to increase the platelet counts in cases of ITP that did not respond to a lower dose, i.e. 50 mg[13].

Ongoing Eesearch

Trials are currently underway to explore the role of eltrombopag in conditions like myelodysplastic syndrome, secondary acute myeloid leukemia after myelodysplastic syndrome, patients of sarcoma receiving adriamycin and ifosfamide, aplastic anemia patients with immunosuppressive-therapy, refractory thrombocytopenia and Wiskott-Aldrich syndrome. Trials are also on to find if eltrombopag can reduce the need for platelet transfusions in patients of chronic liver disease who undergo elective procedures.

Table II. Important trials of Eltrombopag.

References	Patient subset	Dosage	Results
Bussel et al 2007 (7)	Placebo controlled RCT 118 chronic ITP Platelets <30,000/μL, Relapsing or refractory ITP	30 mg, 50 mg, 75 mg for 42 days	Platelets > 50,000 was achieved in 28% (30 mg), 70% (50 mg) and 81% (75 mg) patients in three groups respectively
Jenkins et al 2007 (12)	73 placebo controlled healthy adults	5, 10, 25, 30, 50, 75 mg for 10 days	No difference in adverse effects between placebo and active drug
Mchutchinson et al 2007 (10)	Placebo controlled RCT 74 HCV related cirrhotic patients with platelets between 20-70.000/μL	30, 50, 75 mg for 4 weeks	Platelets > i lakh/μL were achived in 75% (30 mg), 79 (50 mg) and 95% (75 mg)
Bussel et al 2009 (13)	Placebo controlled RCT in chronic ITP	Dose of 50 mg for 3 wks, increased to 75 mg in nonresponders	59% pts on eltrombopag 50 mg achieved platelet count ≥50.000. Amongst nonresponders 29% dose escalation

Contraindications

There are no known contraindications to the use of eltrombopag.

Interactions

Although the data on possible interactions is limited the fact that eltrombopag is metabolized via CYP 1A2 and 2C8 may lead to possible interactions with other drugs which use these pathways like: ciprofloxacin, fluvoxamine, omeprazole, tobacco, trimethoprim, rifampin. Therefore, caution is neede when such drugs are co-prescribed.

Adverse Effects

The various adverse events noticed with eltrombopag are mild and don't differ with the placebo group. Headache is the most common adverse effect seen with eltrombopag which has prevalence similar to that seen in the placebo group[7]. Of the 485 patients put on eltrombopag and studied in 4 different randomised trials 7 developed cataract and previously existing cataract worsened in 5 of the subjects. Even this cannot be completely attributed to eltrombopag alone as all the patients who developed these cataracts also had a history of corticosteroid use. Thromboembolism and pulmonary embolism are seen, but very rarely, in a patient on eltrombopag and that too in patients who have an underlying thrombophilic state[14]. Increase in ALT and hyperbilirubinemia have also been reported as side-effects of eltrombopag. Liver functions should be regularly monitored. Bone marrow reticulin deposition is seen with the prolonged therapy. Bone marrow fibrosis should be suspected if morphological changes appear in the peripheral smear or if cytopenias appear. After the discontinuation of eltrombopag the platelet levels may fall below baseline in a few patients. Increased rates of tumor progression have been seen with the use of erythroid stimulating agents. The same happening with the use eltrombopag is a fear that remains unproven, although there are reports of progression of myelodysplastic syndromes to acute myeloid leukemia with romiplostim[9,11].

Special Populations

Ethnicity. In patients of East Asian ancestry, exposure to eltrombopag is higher and, therefore, the starting dose in this population should be 25 mg. A higher exposure is also described in African-American patients[9].

Pregnancy. It is a pregnancy risk category C drug, and can be used if potential benefits to mother justify its use[9].

Hepatic Impairment. Clearance of drug is reduced to half in patients with hepatic impairment, so doses should be adjusted. Starting dose in such patients should be 25 mg. If there is an increase in serum aminotransferases or bilirubin the drug should be stopped.

Renal Impairment. No specific guidelines to aid the administration of eltrombopag are available in renal insufficiency.

Adolescents and children. The efficacy and safety has not been established in children and adolescents.

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