Incidence Of Primary Immune Thrombocytopenic Purpura:
- Children 5-6/100,000 / year
- Adults 10/100,000 / year
- Elderly increased

Thrombopoietin In Primary ITP:
- Thrombopoietin (TPO) is a hormonal regulator of Thrombopoiesis

Plasma endogenous TPO levels:
- In ITP endogenous TPO levels are not increased or only marginally increased.
- In Aplastic anemia are markedly increased.

Treatment Of Primary ITP With Stimulation Of TPO Receptor:
- Recombinant Thrombopoietin was abandoned as healthy volunteers developed thrombocytopenia due to development of Anti Thrombopoietin Antibodies.
- TPO mimetic agents Romiplostim & Eltrambopag are TPO agonist with dissimilar structure to TPO and do not form Autoantibodies.
- Romiplostim (Amgen Nplate) is a synthetic peptibody made of 4 peptide made of 14 amino acid residues fused with Fc fragment of IgG. (See fig 2.)
- Eltrambopag (Promacta, GlaxoSmithKline) (in India Revolade) is a small nonpeptide molecule that binds the transmembrane region of TPO receptor. (See fig 1.)
- Both activate the JAK-STAT & MAP Kinase pathway to Stimulate platelet Production.

Fig 1: Show the TPO receptor & Site of action of Romiplostim & Eltrambopag
Fig 2: Show the structure of Romiplostim

Pharmacodynamic Response:
- Romiplostim & Eltrombopag give similar pharmacodynamic response with rise in platelets on day 5 to 8, peak by day 12 to 16 and fall to baseline by day 28.

Response To TPO Mimetics In Primary ITP:
- **Romiplostim**: Phase 3 studies in Adult with refractory immune thrombocytopenia with platelet count < 30,000/cumm.
- Risk of life threatening Bleeding in ITP is confined to those with platelet count < 10,000 or between 10,000 to 20,000/cumm.
- Romiplostim 2 trials, Placebo controlled phase 3 of 24 weeks duration. One enrolled 63 splenectomized cases & other 62 nonsplenectomized cases. Primary end point was durable response defined as Platelet count > 50,000/cumm for at least 6 of the last 8 wks.
- Primary End point achieves in 38% splenectomized group & 61% of nonsplenectomized patients. In the placebo arm none of the splenectomized patients & 5% of nonsplenectomized patients achieved primary end point.
- In an ongoing open label Extension Study involving 292 patients;
  - 94.5% achieved a platelet count of at least 50,000/cumm
  - 50% have platelet count > 50,000/cumm at least 90% of all visits at a median follow up of 78 wks.
- **Eltrombopag**: FDA approval on basis of two 6 wks placebo controlled clinical trial & initial result of open label extension study.
- Primary efficacy measurement was achievement of platelet count of at least 50,000/cumm on day 43.
- In dose adjustment study enrolling 118 patients; those receiving doses of 50 to 75 mg were more likely to achieve this end points.
- In a subsequent phase 3 trial enrolling 114 patients, Eltrombopag was given at a dose of 50 mg/day and 59% patients achieved platelet count of 50,000/cumm on day 43. In the placebo arm only 16% could achieve the primary end point.
- In an open label extension study involving 299 patients who had previously participated in Eltrombopag study, 87% achieved a platelet count of 50,000/cumm during treatment.

Do TPO Mimetic Drugs Reduce Bleeding In Primary Immune Thrombocytopenia?
- **Romiplostim Extension Study**: incidence of Mod to severe bleeding decreased from 23% to 12% in first 24 wks, & then to 6% in the extension during wks 24 to 48.


- **Eltrambopag Extension Study**: incidence of any bleeding decreased from 56% at baseline to 16% by week 52 & 20% by week 104.

**When To Treat In ITP?**
- Platelet count < 10,000/cumm in a non-bleeding patient most experts will treat.
- Platelet count < 20,000/cumm with moderate to severe bleeding.

**What Are The Options For Treatment?**
- First line Treatment: Steroids, IVGG, and I.V. Anti-D.
- Second line options: Splenectomy, Rituximab, Dapsone, Immunosuppressive therapy like Azathioprine, Cyclosporine & others.
- TPO mimetic will most likely be used in a patient of Primary ITP with platelet counts < 20,000/cumm with significant bleeding who has failed primary & secondary line therapy including Rituximab. It may also be an option for those who will want to avoid splenectomy.

**TPO Mimetics Dosing And Monitoring:**

- **Romiplostim**:
  - Starting dose 1µg/kg/week SC.
  - Dose adjusted as per therapeutic platelet response.
  - Mean dose is 3 to 4 µg/kg/week.
  - Maximum dose: 10 µg/kg/week.
  - Romiplostim is available as 250 µg to 500 µg/vial as a lyophilized powder.

- **Eltrambopag**:
  - Starting dose: 50 mg Orally once a day.
  - Increase dose as per response to maximum 75 mg orally
  - Minimum dose 25 mg once daily

**Dosage Modifications:**
- Hepatic injury and in patients of Asian ethnic origin starting dose should be 25 mg.
- In India patients starting dose is 25 mg once daily.
- Eltrambopag should be taken 1 or 2 hrs before meals
- Avoid taking it with in four hrs of taking Antacids, milk or milk products, supplements containing polyvalent cations like calcium, magnesium, Iron, Selenium, Zinc and aluminum.

**Monitoring Of Response:**
- Platelet count weekly
- Once stable platelet count > 50,000/cumm for 4 wks achieved; Platelet count monthly.
- Withhold Treatment if platelet count between > 200,000 to 400,000/cumm.
- In our set up it is best to maintain platelet count at and around 50,000/cumm
- In patients on Eltrambopag, monitor LFT every 2 weekly during dose adjustment phase and once monthly once dose stabilized.
- On stopping treatment 8 to 10% patients can develop increased risk of bleeding in the first 4 weeks after stopping treatment.
- In most patients typically pretreatment baseline platelet counts may be reached after several weeks of stopping drug.

**Side Effects Of TPO Mimetics:**
- Most common side effects of TPO mimetics are Headache, Nausea, Vomiting, Fatigue, Diarrhoea, arthralgia & Nasopharyngitis.

**Hepatotoxicity:**
- 11% of Eltrambopag patients had elevated aminotransferases 3 times above normal levels. This effect may disappear on continuation of medication.
- Discontinue Eltrambopag if elevated aminotransferase is,
  - Progressive or
  - Persistent for > 4 weeks or
  - Accompanied by elevation of Serum Bilirubin or
  - Accompanied by clinical evidence of liver injury or evidence for hepatic decompensation.
- Romiplostim does not have any hepatotoxicity.

**Thromboembolic Events:**

- **Romiplostim**
  - In 291 patients, 25 thrombotic events occurred in 17 patients.
Eltrambopag:
- In 299 patients, 21 thromboembolic events occurred in 16 patients.
- Frequency of thromboembolic events did not increase with duration of therapy.
- Most patients had an additional risk factor for thromboembolism.

Bone Marrow Fibrosis:
- Bone Marrow fibrosis was seen in 3 patients in an extended Eltrambopag study, involving 83 patients on BM Biopsies at 12 & 24 mths.
- The increase in BM reticulin appears to be reversible on discontinuation of medication.

Overdose:
- Eltrambopag: Use cation containing preparation like Calcium, Aluminum or Zinc to limit absorption of Eltrambopag.
- Monitor platelet count.

Malignancies & Progression of Malignancies:
- TPO-Receptors are also expressed on surface of the cells of Myeloid lineage; thus a theoretical concern for progression of MDS.

Cataract:
- Seen in animal studies with Eltrambopag.

Dosage Adjustment:
- No dose adjustment for Eltrambopag is required in renal failure.

Pregnancy & Lactation:
- Animal Studies show significant reproductive toxicity with Eltrambopag.
- Eltrambopag must be avoided in pregnant women, lactating women & women in childbearing age group not practicing contraception.

Drug Interactions:
- Caution when co administering with Methotrexate & Topotecan.
- Lopinavir / Ritonavir decrease levels of Eltrambopag.

Discontinuation of Drug:
- STOP Eltrambopag if No rise in platelet count from baseline 4 weeks after starting treatment

Dilemmas In Treatment Of Primary ITP:
- When to start treatment is a difficult issue as platelet count & clinical bleeding do not always correlate.
- Is the need to take drug lifelong & what are the long-term toxicities?
- Intermittent dosage scheduling is tried as this would minimize exposure to drug and will be cost effective too.
- Many patients wanting to avoid splenectomy would prefer to take a drug.
- Splenectomy is an established second line treatment in Adult ITP but other second line treatment like immunosuppressive drugs do not have robust data.
- Failure of response to TPO mimetic should make one look for alternative diagnosis; one will have to rule out IBMFS (Inherited Bone Marrow Failure Syndromes)
- Use of TPO mimetics in secondary Immune thrombocytopenia need to be studied.
- There is no data of use of TPO mimetics in children and adolescents.

What Do The Guidelines Say?

ASH ITP 2011 Guidelines
- ASH recommends the use of thrombopoietin-receptor agonists in adult patients at risk for bleeding that have a relapse after splenectomy or splenectomy is contraindicated & has no response to at least one other therapy.
- Adult patients at risk for bleeding, who have not had a response to one line of therapy and have not undergone splenectomy.

- TPO mimetics is an option for treatment for adult ITP patients as second-line therapy and also as an option in those whom first-line and other second-line therapies have failed.
- Neither guideline recommended the use of thrombopoietin-receptor agonists in children.
- Use in Children will be off label on compassionate grounds only till data accrue.

“ Well Guide lines are guidelines and one need to evaluate their applicability independently in their own set up”
At all times an appropriate approach in Primary ITP need to be minimalistic rather than just chasing the platelet count.

Do Not Forget the age old dictum; “Rx The Patient And Not The Platelet Count Only”

What one needs is safe platelet counts at a minimum cost & minimum side effects.

**Considerations In Indian Patients With ITP:**
- In India we will have the advantage of starting at a lower dose of 25 mg;
- We need to keep platelets at around 30,000 to 50,000 / cumm.
- We need a safe platelet count & do not need a normal platelet count. A safe platelet count is 30,000/cumm.
- We can use alternate day or twice a week dosing once stable response achieved as Eltrambopag has longer half-life.
- We can foresee greatest use of TPO mimetics in postponing Splenectomy in India.

**TPO Mimetics Other Considerations:**
- Use of TPO mimetics, as first line is not recommended.
- Use of TPO mimetics, in secondary thrombocytopenia may be seen in absence of availability of efficacy data.
- Use of TPO mimetics, in pregnancy is contraindicated as the TPO mimetic cross the placenta.
- Use of TPO mimetics in an emergency cannot be recommended as it takes a long time to response.

**Availability in India:**
- Eltrambopag is available as Revolade in India, in 25 mg and 50 mg strength.
- 25 mg tablet costs Rs 750 per tablet while 50mg costs Rs 1500 per tablet.
- One box of Revolade has 4 strips with each strip having 7 tablets.
- One box contains tablets for 28 days.
- Monthly cost for 25 mg tablet is Rs 21,000/-. 
- Monthly cost of 50 mg tablet is Rs 42,000/-.

**Reference:**
Thrombopoietin-Receptor Agonists for Primary Immune Thrombocytopenia
Paul Imbach, M.D., and Mark Crowther, M.D.