Eltrombopag treatment and other similar drugs in Idiopathic thrombocytopenic purpura

Gabriel Gaman, Amelia Gaman, Ica Alexandru, Alina Oprea
UMF Craiova
Municipal Hospital "Filantropia" Craiova

TRA (Thrombin Receptor Agonist)

Romiplostim and eltrombopag, have been approved by the Food and Drug Administration (FDA) for use in patients with primary ITP who require treatment after an initial course of corticosteroids. In some parts of the world, approval is restricted to patients needing therapy after splenectomy.

Romiplostim is a "peptibody" composed of four identical peptides that bind to the thrombopoietin receptor cMPL fused to an Fc fragment to prolong its half-life. It is administered weekly as a subcutaneous injection (1–10 μg/kg). In two parallel, placebo-controlled, double-blind randomized phase III trials, the study drug was given to 63 splenectomized and 62 non-splenectomized patients for 6 months. The primary efficacy end point, a platelet count of 50 x 109/L or above for at least 6 of the last 8 weeks of the study in the absence of rescue therapy, was achieved in 61% of non-splenectomized patients and in 38% of splenectomized individuals receiving romiplostim, and in only 1 of 42 subjects receiving placebo. Many romiplostim-treated patients reduced or discontinued concurrent ITP therapy, primarilycorticosteroids, and reported improved quality of life. In an ongoing open-label extension study, most patients, some approaching 5.5 years of treatment with romiplostim, have sustained their platelet response.

Eltrombopag is formulated for oral administration at a dose of 25 to 75 mg/d. It must be taken 1 h before or 2 h after a meal, and should not be taken within 4 h of medications or products containing polyvalent cations such as antacids, dairy products, or mineral supplements. Initial dosage is reduced by 50% in patients of southeast Asian origin. The dose of rosuvastatin or other substrates of the OATP1B1 transporter, which is inhibited by eltrombopag, may require adjustment. Efficacy similar to romiplostim has been observed in clinical trials of eltrombopag. In a phase III study lasting 6 weeks, 114 subjects were randomized to receive eltrombopag or placebo. The primary end point, a platelet count of 50 x 109/L or above at week 6, was achieved in 59% and 16% of eltrombopag-treated and placebo-treated subjects, respectively. Patients receiving eltrombopag experienced less bleeding, less need for rescue medication, and a reduction in concomitant treatments. Similar findings were documented in a 6-month phase III trial. Sustained responses of up to 2 years in an ongoing open-label extension study have been reported.

Romiplostim and eltrombopag are generally well tolerated. Increased bone marrow reticulin has been observed in a few patients within 1 year of initiating TRA therapy. However, loss of response associated with evidence of a myelophthistic picture is rare and appears to be reversible in most cases. Additional long-term studies are needed to elucidate the incidence and natural history of TRA-induced bone marrow fibrosis and to compare these findings with the effects of other ITP therapies on bone marrow histology.

Rebound thrombocytopenia to levels below those at the onset of treatment was noted in approximately 10% of patients who discontinued either romiplostim or eltrombopag in clinical trials. Gradual withdrawal of TRAs, careful surveillance, and possibly preemptive introduction of concomitant ITP medications may prevent or ameliorate this toxicity.

To date, there is no compelling evidence that either TRA increases thromboembolic complications in patients with ITP. In a pooled analysis of all studies of romiplostim, the incidence of thrombosis did not differ among those treated with study drug and those receiving placebo (8 vs. 10 events/100 patient-years, respectively). In a pooled analysis of studies of eltrombopag in ITP, 17 eltrombopag-treated patients suffered thrombotic complications over 377 patient-years of exposure. Although no events were documented in placebo-treated subjects, the exposure of this cohort was limited to only 26 patient-years. Most TRA-associated thromboembolic events have occurred in patients with preexisting atherosclerosis or thrombotic risk factors, often in the setting of a low or normal platelet count. In light of recent evidence that eltrombopag may increase the risk of venous thrombosis in patients with hepatitis C, and that ITP itself may be prothrombotic in some patients, additional study of the incidence of TRA-associated thrombosis and identification of potential risk factors is warranted.

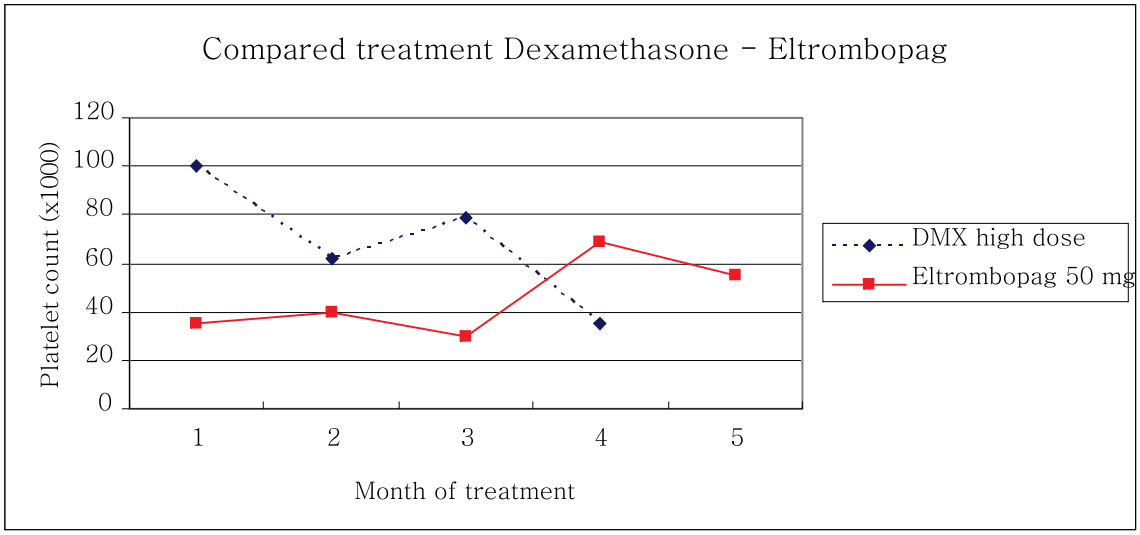
Thus far, data regarding the risk of leukemogenesis with TRA therapy are reassuring. In the controlled trials of romiplostim and eltrombopag, the incidence of hematologic neoplasm was low and similar in the

treatment and placebo groups. In studies of patients with myelodysplastic syndrome-associated thrombocytopenia, romiplostim was associated with a transient and reversible rise in circulating blasts in a minority of patients, but the rate of leukemic transformation did not differ between romiplostim- and placebo-treated subjects.

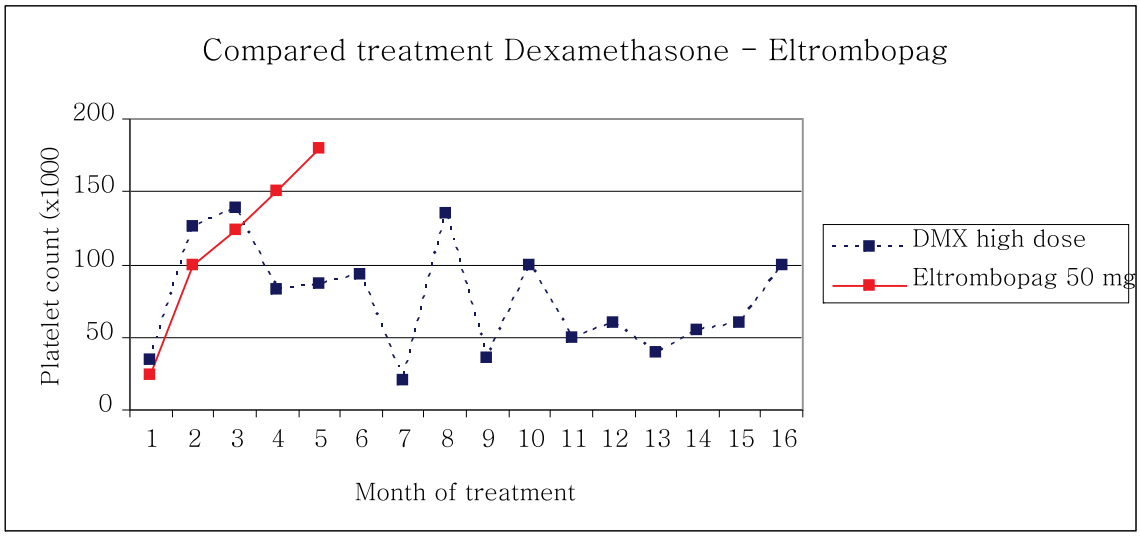
Hepatobiliary laboratory abnormalities were detected in 13% of eltrombopag-treated patients, prompting a black-box warning that calls for regular monitoring of liver function tests. Cataract formation was observed in preclinical testing of eltrombopag in juvenile rodents at doses several times higher than the human clinical exposure. Until more is known regarding the risk of cataract development in humans at clinically approved doses of eltrombopag, periodic ophthalmic examinations are advisable.

We had to study a batch of 5 pacients with Idiopathic thrombocytopenic purpura, relapsed or refractory to treatment with Prednisone and then high dose Dexametasone (40 mg/day x 4 days), an application to 21 days, 6 such applications.

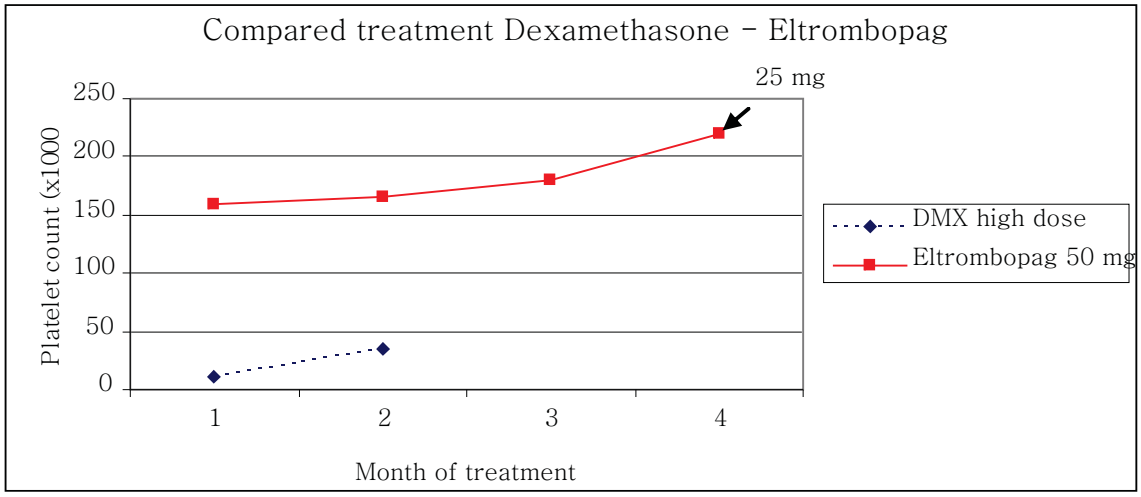
We present graphically the evolution under the treatment with Eltrombopag 50 mg/day of the 5 pacients.



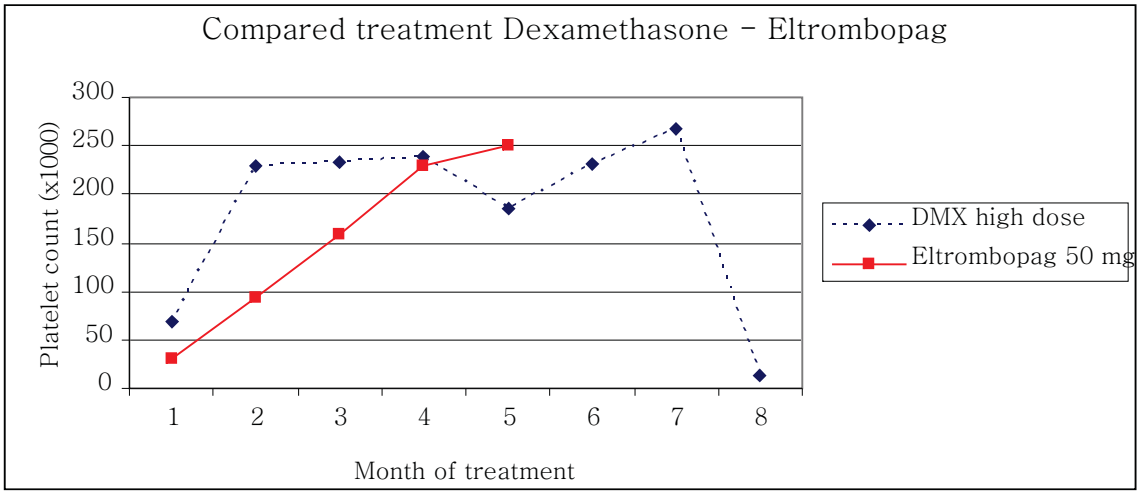
I.D patient, 62 years old, male, with initial platelet count of 100.000/mm³, treated initially with high dose Dexamethasone, then Eltrombopag 50 mg/day, for 4 months. Eltrombopag therapy proved ineffective.



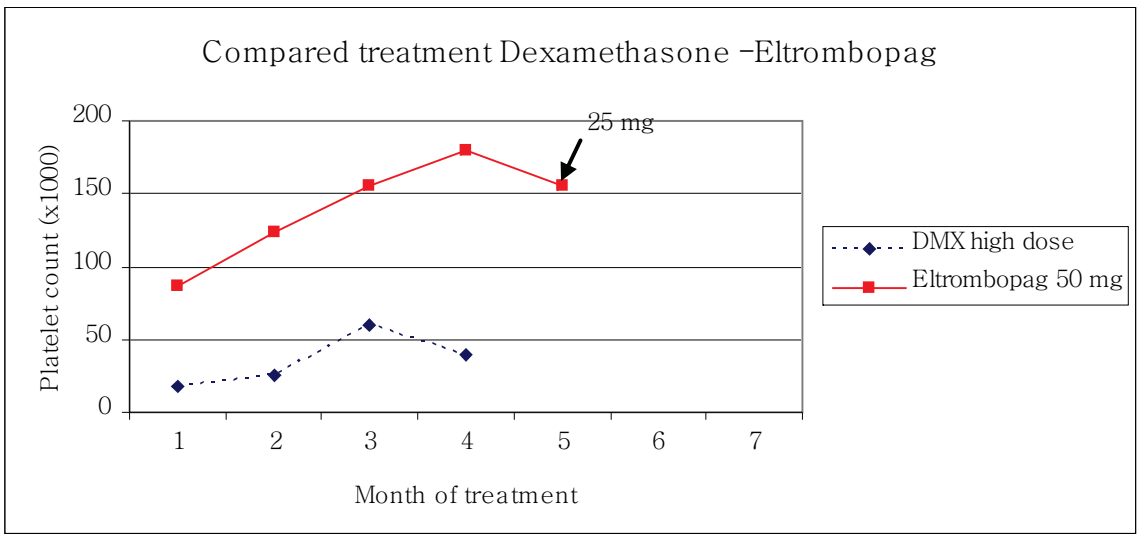
S.G patient, 70 years old, female, with initial platelet count of 34.000/mm³, treated with Dexamethasone, but suffered several relapses.After 4 months of treatment with Eltrombopag 50 mg/day, patient reached a total of 180.000/mm³ and will continue Eltrombopag therapy at a dose of 25 mg/day.



Patient D.F, 30 years old, female, with initial platelet count of 11.000/mm³, 2 months treated with Dexamethasone, followed treatment with Eltrombopag 50 mg/day, reaching a platelet count of 220.000/mm³ after 4 months of treatment. He will continue therapy with Eltrombopag at a dose of 25 mg/day.



Patient N.N, 67 years old, female, with initial platelet count of 68.000/mm³, initially responded to treatment with Dexamethasone, but suffered two relapses; following treatment with Eltrombopag 50 mg/day, reaching a platelet count of 250.000/mm³ after 4 months.



Patient P.P, 60 years old, female, with initial platelet count of 18.000/mm^3, following initial treatment with high dose Dexamethasone, but not responding to therapy; following treatment with Eltrombopag 50 mg/day, and 4 months after is achieving a platelet count of 180.000/mm^3.

Conclusions

1. A batch of 5 refractory or relapsed patients were initially treated with Eltrombopag 50 mg/day for a period of 1-4 months; 4 of them are still in complete remission of disease, one patient was refractory to this treatment.
2. Eltrombopag treatment in the initial dose of 50 mg/day was beneficial in 80% of cases, patients that are still in complete remission, a single patient so treated was reluctant, as a last resort benefiting the splenectomy.
3. Eltrombopag treatment led to the normalization of platelet count in a period of 21-32 days for 80% of patients.
4. Eltrombopag did not induce unwanted side effects and did not interact with medications used to treat such patients.
5. The disadvantage of Eltrombopag treatment consists of high drug prices.
6. We believe that the management of patients with ITP should be done "in steps" for relapsed or refractory patients, using Eltrombopag as an effective alternative. In the future, we plan a study on a larger group of patients, to assess more accurately the results of Eltrombopag therapy in ITP, considering that the drug will enter the free scheme by National Health Insurance House.

References

1. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008;371:395–403
2. George JN, Mathias SD, Go RS, et al. Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomized, placebo-controlled trials.Br J Haematol. 2009;144:409–415
3. Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M and Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood. 2009;113:2161–2171
4. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373:641–648
5. Cheng G, Saleh MN, Bussel JB, et al. Oral eltrombopag for the long-term treatment of patients with chronic idiopathic thrombocytopenic purpura: results of a phase III, double-blind, placebo-controlled study (RAISE) [Abstract]. Blood. 2008;112:400–
6. Saleh MN, Bussel JB, Cheng G, et al. Long-term treatment of chronic immune thrombocytopenic purpura with oral eltrombopag: Results from the EXTEND study [Abstract]. Blood. 2009;114:682–
7. Cuker A, Chiang EY and Cines DB. Safety of the thrombopoiesis-stimulating agents for the treatment of immune thrombocytopenia. Curr Drug Saf. 2010;5:171–181
8. Liebman H, Henry D, Lefrere F, et al. Long-term safety profile of romiplostim in patients with chronic immune thrombocytopenia (ITP). Blood. 2008;112:Abstract 3415
9. Bussel J, Cheng G, Saleh M, Vasey S, Aivado M and Brainsky A. Thromboembolic events observed in eltrombopag clinical trials in chronic immune thrombocytopenic purpura [Abstract]. Blood. 2009;114:2423–
10. Aledort LM, Hayward CP, Chen MG, Nichol JL and Bussel J. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. Am J Hematol. 2004;76:205–213
11. Cuker A. Toxicities of the thrombopoietic growth factors. Semin Hematol. 2010;47:289–298