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Title: Treating ITP by increasing platelet production

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The initial demonstration that ITP was caused by platelet destruction was in the dramatic experiments 50 years ago of Dr. William Harrington and his colleagues in St. Louis who transfused themselves with blood from patients with ITP. Their platelet counts dramatically decreased. We told this story in the September 1999 issue of *The Platelet*. These experiments first demonstrated that ITP was due to the rapid destruction of circulating platelets; later the platelet destruction was shown to be caused by autoantibodies. However, this is not the only cause of low platelet counts in ITP. It has been demonstrated that bone marrow production of platelets is not as effective as it should be. The bone marrow has a great capacity to increase platelet production, perhaps as much as 7 times the normal rate. Yet in many patients with ITP bone marrow production of platelets is just the same as normal, or even slightly reduced. Some autoantibodies in ITP affect the bone marrow megakaryocytes, the large cells which produce platelets, as well as circulating platelets. In addition, blood levels of thrombopoietin (often abbreviated as TPO) are not increased in many patients with ITP. TPO is the body's hormone that stimulates megakaryocyte development and platelet production. In other conditions with low platelet counts (for example, patients with aplastic anemia, a disorder in which the marrow is empty and fails to make any of the blood cells), TPO levels in plasma can increase 10-fold in an attempt to increase platelet production.

The goal of all current treatments for ITP is to prevent the abnormally increased platelet destruction. However, a new advance is to use drugs that mimic the effects of TPO and stimulate megakaryocytes to produce more platelets, the idea being that increased platelet production can "overwhelm" the autoantibody-induced platelet destruction. When TPO became available as a possible treatment for ITP, many hematologists thought it would not work. They thought that bone marrow platelet production could not be further stimulated, or if it could be increased the platelets would be rapidly destroyed and the platelet count would not change. However clinical trials over the past three years have demonstrated the effectiveness of these agents.

Two TPO-like drugs are currently in clinical development in both the U.S. and Europe, and it seems that both will meet requirements for approval by the regulatory agencies. One is made by Amgen and is currently called AMG 531; the other is made by GlaxoSmithKline and is called eltrombopag. We can be sure that these drugs will have simpler names when they are approved and for sale. AMG 531 is given as a subcutaneous injection once a week. Patients can potentially give it to themselves. Eltrombopag is a tablet taken once a day. Both agents are effective in increasing platelet counts in most patients with ITP. They even work in some patients in whom steroids, splenectomy, and other immune suppressive agents have all failed. Since the goal of treatment is only to achieve a safe platelet count, such as above 30,000-50,000 per microliter, these agents can be adjusted to maintain platelet counts in a safe range. The value of these agents has been demonstrated in some of the patients we have studied with AMG 531. In some of the initial trials, before the best dose was established, the platelet count in one of our patients increased to over 800,000 per microliter after AMG 531 therapy. Although these very high platelet counts for a brief time are not dangerous, the optimal dose needs to be established for each patient. This is like insulin treatment for diabetes, where each patient has to adjust their dose to keep their blood sugar in the proper range.

The important and exciting thing about these new TPO-like drugs is that they provide more treatment options for patients with ITP. We are impressed that major pharmaceutical and biotech companies are responding to the unmet needs of ITP patients. Once these TPO-like drugs are widely available, it will probably remain unclear for awhile when they may best be used. In adults with ITP, they may help to avoid the toxicity of steroids and delay the need for splenectomy, or help to keep platelet counts at a safe level if splenectomy has failed. In children, these agents may be easier to use and have fewer side effects than current medications, and they may help to maintain safe platelet counts until the ITP goes away and a remission is achieved. Perhaps

even in adults, if splenectomy and treatment with immunosuppressive drugs can be postponed, spontaneous remissions may occur, similar to what we see more commonly in children.

What must be remembered is that these new TPO-like drugs don't cure ITP and probably don't even modify its course. Their value is that they may help maintain a safe platelet count while ITP persists. In this way these TPO-like drugs are like insulin treatment for patients with diabetes. Insulin maintains the blood sugar in a safe range without changing the course of the disease. Just like insulin has changed the lives of diabetics, we hope these new drugs will be able to improve the lives of patients with ITP.