The ITP Support Association Platelet Reprint Series

No. 39 – Who Needs the New TPO Drugs

American Perspective reprinted from: **Sept 2011**

Title: **Who Needs the New TPO Drugs for ITP?**

Author: **James N. George, M.D., George R. Buchanan, M.D.**

The recent development of a new class of drugs for the treatment of ITP has been important for many reasons. Most importantly, these new drugs have provided effective treatment for many patients who had failed to achieve a safe platelet count with all previous treatments. Second, the development of these drugs has been important for understanding why platelet counts are low in patients with ITP.

The first two drugs of this new class, romiplostim and eltrombopag, demonstrated that stimulation of the bone marrow to increase platelet production can be effective for increasing the platelet count in patients with ITP. For many decades, it had been assumed that the principal and perhaps only reason for low platelet counts in ITP was the increased platelet destruction by autoantibodies. All treatments for ITP were aimed at reversing this increased platelet destruction. Drugs such as steroids suppress the production of autoantibodies; IVIG and anti-D block the removal of the antibody-coated platelets from the circulation; splenectomy removes the major organ where antibody-coated platelets are destroyed. The new drugs were patterned after the body's normal hormone that stimulates and regulates platelet production, thrombopoietin, abbreviated at TPO. The initial clinical trials for the development of these new TPO-like drugs were dramatic. Some patients who had failed to respond to multiple treatments for ITP, including splenectomy, had dramatically increased platelet counts. With increasing experience it is clear that most, perhaps as many as 85% of patients, can respond to these agents.

A third part of this story is the increased attention focused on ITP patients by the pharmaceutical companies who have developed these new drugs. The clinical trials to develop these drugs involved hundreds of ITP patients; the results demonstrated impressive benefits; the results were published in prominent medical journals. Never has ITP been so prominently featured in the medical news. This new spotlight of attention is bringing the stories of ITP patients to many people who previously didn't know about ITP. This makes ITP more familiar and therefore makes life better for patients with ITP because they feel less isolated. They can feel the comfort that there is recognition of their illness and that there is active scientific progress.

Now that these drugs are available in many countries, the issue is to understand where they should fit into the sequence of treatments for patients with ITP. In this article, we address the appropriate use of TPO drugs in adults with ITP; we'll discuss the issues of the use of these drugs for children in another article. Which patients have the greatest need for these new drugs and can have the greatest benefit? The answer to this question is clear: patients who have failed to respond to initial treatment with steroids, who may have little or only transient responses to IVIG or anti-D, who have failed treatment with stronger immunosuppressive drugs like rituximab and failed to respond to splenectomy. These are the patients who have the greatest need and who can achieve the greatest benefit. For these patients, there are few other treatment options and most have little chance for success and lots of risks for complications. For these patients, the new TPO drugs bring a new era of hope.

But since the TPO drugs are effective, should they be used sooner in the sequence of treatments? Should they be used to avoid intensive immunosuppression with rituximab? Should they be used to avoid need for splenectomy? These are the questions that are asked in new clinical trials. What are the disadvantages of using these drugs before rituximab and splenectomy? First, these agents only support increased platelet counts while they are given. They do not affect the ITP itself; they only shift the platelet count to a higher level by increasing production. They need to be taken indefinitely, which may mean forever. Although there are stories that adults with persistent ITP may have a spontaneous

remission from ITP, similar to the common and expected spontaneous remissions that occur after several months in most young children, these rarely occur. In almost all adults, it is assumed that ITP is a long-term illness, if not permanent. So then the issue can be described as taking a drug forever to maintain a safe platelet count versus attempting treatments that have a substantial chance for curing ITP. For example, over 50 years of experience tells us that two-thirds of patients who have a splenectomy achieve a normal platelet count with no further treatment and with only a small risk for recurrence. The cure from rituximab is less but still probably exceeds one-third of patients. Of course there are risks with splenectomy and rituximab; we've discussed these before in these articles. Although the risks of splenectomy and rituximab are important, the risks of lifetime administration of TPO agents are unknown. A note of caution for the use of the TPO drugs come from the experience over the last 25 years with the EPO drugs, that are patterned on erythropoietin, the natural hormone that stimulates red blood cell production. EPO drugs have been widely used in patients with kidney failure and cancer, but increasing evidence indicates that they have increased the risk for heart attack and stroke. Since it has taken 25 years for these adverse effects to become recognized with the EPO drugs, it is appropriate to be cautious about the long-term effects of the TPO drugs.

Therefore the appropriate use of the TPO drugs in patients with ITP remains undefined. This has caused extensive debate by drug licensing agencies and by NICE (National Institute for Health and Clinical Excellence) in the UK. These agencies are charged with balancing the benefits of drugs with their risk and also with their costs. The TPO drugs are extremely expensive; taking them for many years is an enormous cost burden. The goal of all regulatory agencies is to make all drugs available for those patients who need them most, but to restrict their use when other standard treatments are available and effective.

So who needs the new TPO drugs for treatment of ITP? Absolutely, patients who have failed treatments with steroids, rituximab and splenectomy need these agents and many will have great benefit. However in young patients with ITP who are otherwise healthy, it is still appropriate to aim first for cure. Cure can be achieved in most patients by splenectomy and in some patients by rituximab. If these efforts fail, the TPO drugs provide the comfort that there is still effective long-term treatment.