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The Promise of Thrombopoietins in the Treatment of ITP

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H&O How has the thinking about idiopathic thrombocytopenic purpura changed in recent years?

DK For a long time it was thought that the major mechanism of idiopathic thrombocytopenic purpura (ITP) involved the production of antibodies against platelets that destroy the platelets in the circulation. This was supposedly accompanied by an increased rate of platelet production by the bone marrow in an attempt to compensate for the thrombocytopenia. In classic ITP, when the bone marrow failed to compensate fully for the platelet destruction, the platelet count fell.

Now we believe that, in addition to the destruction of platelets by antibodies, these antibodies might also decrease the ability of the megakaryocytes in the bone marrow to respond appropriately to the need to make more platelets. Instead of the bone marrow markedly increasing its production of platelets, platelet production may only be minimally increased or normal. This is important because the traditional therapies for ITP, such as splenectomy and steroids, have been directed toward decreasing the destruction of platelets; with this new understanding, we now believe that a drug that stimulates the marrow to make more platelets might be effective. A fairly new class of drugs called thrombopoietins have this effect. The theory behind why thrombopoietins might be effective in this disease involves the belief that we may not have to correct the destruction of platelets but simply increase platelet production.

H&O Does that mean that previous therapies for this disease were not as effective?

DK No, prior therapies such as splenectomy and steroids have been quite effective in controlling the destruction of

platelets and increasing the platelet count. While splenectomy controls the destructive process in about two thirds of patients, there are risks associated with surgery. Steroids can also control the destructive process, but have many undesirable side effects; once stopped the thrombocytopenia usually returns. Except for splenectomy, all medical therapies can improve the platelet count but do not cure the ITP.

H&O When was thrombopoietin developed?

DK Our group and others first sequenced and cloned thrombopoietin in 1994. In fact, 5 different groups all reported the same results within in a 3-month period.¹

Thrombopoietins were studied in many oncology trials in the mid to late 1990s, but they did not have a significant effect in bone marrow transplantation or in leukemia; they had a modest effect in reducing the need for platelet transfusions in people who received standard chemotherapy. This relative lack of success, in addition to an antibody that developed against one of the thrombopoietins,² led to a 2–3 year period in which there was little research conducted on this class of drugs.

However, a number of researchers believed that there might be nononcologic uses for these molecules in patient groups that had low platelet counts. ITP was selected as a potential target, and the first studies conducted in this area were 2 small trials: Dr. Larry Rice reported in the *American Journal of Hematology* on a patient who has been treated with an early version of thrombopoietin for 7 years,³ and a Japanese group published in *Blood* 4 years ago their findings in 4 patients who also responded to the earlier version thrombopoietin.⁴ Both of these studies were completed before the antibody issue was fully identified.

H&O Were more advanced thrombopoietins then developed?

DK Newer thrombopoietins have since been developed that do not have the same problems with antibodies. Three years ago we started doing the first studies in humans with a molecule called AMG 531 (Amgen).

There were 2 types of thrombopoietin molecules in the 1990s: recombinant human thrombopoietin (rhTPO), made by Genentech and Pharmacia, and

pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF), made by Amgen.¹ Both these molecules were studied extensively in patients treated with chemotherapy and bone marrow transplantation. However, it was found that antibodies were made against PEG-MGDF, which led to a hiatus in research on both types of molecules.

The 2 most significant molecules developed in recent years, which do not appear to be antigenic, are AMG 531, which is a genetically engineered peptide mimetic, or a peptide that looks like thrombopoietin, and SB-497115 (GlaxoSmithKline), which is an oral small molecule that actually binds and activates the thrombopoietin receptor.⁵ Both of these molecules are being studied in ITP right now.

H&O Will they be superior to rHTPO?

DK “Superior” may not be the best way to describe them; they probably have no better biologic effect compared with the earlier thrombopoietins, but they will probably have less risk of developing immune problems against the molecule. In addition to AMG 531 and SB-497115, there are several other thrombopoietic molecules currently in the pipeline.

H&O What is the mechanism of action of AMG 531?

DK This molecule is a modified FC portion of the immunoglobulin molecule. It contains 4 peptides that bind to the thrombopoietin receptor and stimulate megakaryocytes to grow and make platelets.

H&O Is there reason to believe AMG 531 might be the most promising of the thrombopoietins currently being developed?

DK AMG 531 is simply further along in development than SB-497115. It is difficult to determine at this stage which one will be better for use in patients with ITP. Both are active in humans and both raise the platelet count in normal humans; however, only AMG 531 has been shown to work in ITP, while SB-497115 is still being studied. A potential advantage of SB-497115 is that it is orally available

It has been shown that AMG 531 makes the platelet count rise in a dose-dependent fashion, sometimes to over a million in normal healthy people.⁶ Two studies of this molecule have been completed, with 3 more underway. Two thirds of patients experienced a response in the phase I trial. A later randomized, placebo-controlled trial showed that over 71% of patients treated with AMG 531 responded, defined by their platelet count rising above 50,000 and doubling from their baseline level.⁷

H&O Are these promising results?

DK These are very promising results. They show activity in ITP that is superior to any drug or treatment so far described.

H&O Has the full promise of this treatment been realized?

DK We are eagerly awaiting the results of a third trial of AMG 531, which has not yet been concluded. This trial includes patients from the first 2 trials, who were allowed to enroll in an open-label study. These patients are now receiving weekly therapy, some for over a year now, and most have maintained their platelet count in a target range—a range in which they have been able to reduce or eliminate all of their concomitant therapies, such as prednisone, and which is not associated with any bleeding. That is very promising.

Before now, many patients with ITP had to remain on corticosteroids, which often have major side effects. Simply discontinuing the use of corticosteroids is an enormous benefit to patients.

H&O Does AMG 531 become less effective with successive cycles?

DK Right now there is no such thing as a cycle of this medication: it's given weekly as a subcutaneous injection. The third study we are conducting is an effort to show long-term benefit, and so far patients have been on the medication for up to a year and have maintained their benefit. We do not know yet if they will lose that benefit 2 or 10 years in the future.

H&O Beyond the third study, are there other data that are required before AMG 531 enters clinical use?

DK There are 2 phase III trials of AMG 531 that have recently started and should be completed within the next 12 months: they compare this agent with placebo in patients who have had a splenectomy and those who have not had a splenectomy.

The most promising aspects of this molecule are that it prevents the need for other morbid therapies such as steroids, and it may allow patients to avoid splenectomy. It has few or no side effects, unlike every other treatment for ITP.

H&O Does that mean its use will improve patients' quality of life?

DK One goal of the current phase III trials is to determine how this drug will improve quality of life. We fully anticipate that the studies will support our anecdotal

evidence that the quality of life for people is going to improve enormously with a weekly injection of this molecule. They can discontinue their other therapies, and they will not have to worry about whether their platelet count is low. In addition, it will be an enormous boost for people to know that there is an effective therapy that may preclude the need for a splenectomy.

On the other hand, this molecule does not reverse the underlying process of ITP—if injections are stopped, the platelet count is going to plummet.

H&O Once this drug is approved, will there be any obstacles to clinicians using it?

DK The benefits of treatment with this molecule should be obvious to clinicians. Patients have also been a driving force in this area, because ITP groups like the Platelet Disorders Support Association are fully involved in the development of this molecule and have been enthusiastic about its use.

This has been an interesting approach to a scientific question that we could have labored with for years: is ITP a problem with platelet production? Most other scientific problems are undertaken in a very arduous fashion, beginning by showing the basic biology in animal models or humans. ITP is a disease in which animal models are not very good, and the human biology is very arduous and

difficult to study, so we took a different approach. We had a theory about the cause of ITP, and we could prove it by determining if a molecule that stimulates platelet production is effective. And that was, in fact, the case.

If this drug is approved for ITP, it will certainly have a large number of uses in other chronic thrombocytopenic conditions.

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