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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

New Drug Therapies for ITP

IDIOPATHIC THROMBOCYTOPENIA PURPURA IS A RARE DISEASE THAT HAS BEEN DIFFICULT TO TREAT, IS A NEW SOLUTION HERE?

Idiopathic thrombocytopenia purpura is a rare disease that has been difficult to treat, is a new solution here. Welcome to The clinician's Roundtable on ReachMD XM 157. I am your host DR. Bruce Blue and joining us to discuss a new generation of treatments for idiopathic thrombocytopenia purpura is Dr. David J. Kuter, Chief of Hematology at the Massachusetts General Hospital in Boston. Dr. Kuter is award certified physician in Internal Medicine, Hematology, and Medical Oncology, and chairs the Heparin-Induced Thrombocytopenia Subcommittee at the NIH Network for Transfusion Medicine and Hemostasis. He is also a professor of medicine at the Harvard Medical School.

DR. BLUE:

Dr. Kuter, welcome to ReachMD.

DR. KUTER:

Thank you Dr. Blue. It is a pleasure to be with you today to talk to you about this new area of research.

DR. BLUE:

So, idiopathic thrombocytopenic purpura or ITP has been classically thought to be a disorder of increased platelet destruction. Why is that the prevailing thought?

DR. KUTER:

Again, ITP or idiopathic thrombocytopenic purpura has been demonstrated back in 1950 to be due to antibodies that bind the platelets and direct them to the spleen where they are destroyed. This is based upon a classic experiment medicine where a clinical investigator named, Harrington actually took blood from patients who had the disorder injected into himself and caused his platelet count to drop. When they purified the material that was being injected to him, it turned out it was antibody he was infusing it to himself causing his platelet count to drop low. So, that has been the classic model of platelet destruction in ITP.

DR. BLUE:

And if we ever used that to try and come up with treatments for the disease over time.

DR. KUTER:

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Most if not all current therapies for ITP are directed solely at affecting platelet destruction. For example, a classic therapy for ITP is to remove the site of platelet destruction, which is the spleen or having a splenectomy. Other therapies have been directed towards making the antibody, which is used in IgG antibody disappear, and those are modalities such as prednisone, chemotherapy and a new drug Rituximab which decreases B cell production of this antibody.

DR. BLUE:

What happens when we do a splenectomy on these patients? Does it work?

DR. KUTER:

Basically, the splenectomy has been a tried and true procedure for many decades. It was the first therapy that was showing to be effective in ITP almost 60 years ago by removing the site of platelet destruction, 80% of patients will have their platelet count respond within the first month. That response is durable up to 10 years and probably 60% of all patients who have ITP.

DR. BLUE:

When the spleen is removed what happens to antibody platelet conjugation? Does it go some place else to get destroyed. Does it just float around and do the platelets work what happens?

Dr. KUTER:

In most patients the antibody does not disappear that binds the platelets once the spleen is taken out. In some patients you can actually show the antibody disappears, as there has been a modest theory that has not been well proven that the spleen may be the major site of antibody production. I personally don't buy that. In situations where people fail to respond to splenectomy, the antibody which is persisting codes the platelets probably to a greater degree and are now cleared by other reticular endothelial organs such as the liver, lungs and other places. So the antibody rarely disappears after splenectomy.

DR. BLUE:

Your diary suggests that ITP is also a disorder of decreased platelet production as well. So what's the research that has led to this conclusion?

DR. KUTER:

Well interestingly back around the 1918 era, a several investigators postulated two theories of ITP with very little experimental data. One investigator thought that ITP as I mentioned before was simply the destruction of platelets probably by the spleen, antibodies not yet being known about them, and the other investigator thought that back in 1918 era, that this is due to the fact the body was not making platelets well. So, the concept of having decrease platelet production ITP dates back to about the 1918 era. It was expanded upon by a very famous hematologist name, Damish Sheck around 1950. He also proposed that many patients with ITP probably had a problem with inadequate increased platelet production ITP, but what has happened recently is that several investigators have shown using what are called platelet kinetic measurements, we label platelets and injected into patients that the production rate is low. In addition, recent studies by McMillan and others have actually shown antibodies which you purify from patient's ITP can actually in tissue culture directly inhibit the growth of the precursor cell, the megakaryocyte that makes platelets, and finally if you give patient's drugs as we will talk it later on that increased platelet production that tends to ameliorate the thrombocytopenia which occurs in this patient group.

DR. BLUE:

So, are these two different diseases? The diseases of increased destruction versus those of decreased production, or is it all one and the same.

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DR. KUTER:

I think whenever we should think ITP as a disorder of both increased platelet destruction, which happens in most people as well as a lack of inappropriate rise in platelet production. So in any one patient, these two things live in some kind of balance, destruction, and production, and in my experience, some patients are probably more profoundly affected by the failure to make platelets and other patients are more profoundly affected by the rapid destruction. So, it is quite a broad-spectrum, but in general we should think of ITP as a disorder in all patients of destruction of platelets and inappropriate production for platelets. The normal compensatory mechanism is not working.

DR. BLUE:

So, for these patients that have ITP, do they make the normal amount of platelets that anybody else would and then some of them get destroyed and then they do not rebound the way they are supposed to, is what I am hearing.

DR. KUTER:

Well I think if you think about with one as the normal production rate, in kinetics studies in ITP patients it has been shown that production rate may rise twofold in some patients, but usually does not change at all in most patients. The maximal compensation that we think people could make is may be a 6 to 10 fold increase rate of platelet production. So most with patients with ITP have a normal rate of production with a slightly increased, but aren't compensating fully as they might otherwise do in _____ situation.

DR. BLUE:

What molecule regulates this platelet production and when was it discovered?

DR. KUTER:

The molecule that regulates platelet production is called thrombopoietin. It was partially to exist back in the 1950s by a researcher in Middle Europe named Killiman, who thought that a molecule like erythropoietin for red cells must exist for platelets meet partially the term thrombopoietin. This led to an amazingly long period of time, almost 40 years before the molecule was identified, purified, cloned in sequence, and that occurred back in 1994. So, after some 40 years of experimentation, we actually identified this molecule and knew it was in 1994. It's the sole regulator platelet production. If you genetically remove this molecule from an animal for example, the platelet count drops to about 10% of normal. There are some individuals who are born without this molecule or its receptor and those individuals they live well, they have low platelets counts, but the counts are about 10% of normal.

DR. BLUE:

And you mentioned a receptor. Where is does that receptor lie?

DR. KUTER:

The receptor for thrombopoietin, we will call the thrombopoietin receptor for these discussions, but it is historically a receptor called the MPO receptor that was identified back in 1992, two years before thrombopoietin was identified. Basically, receptor was found to be present in an oncogenic virus that caused bone marrow problems in mice. When that receptor was cloned and sequenced it was found to be a new receptor and it was found primarily in megakaryocytes and platelets. We now know that the receptors present at a very low level in many bone marrow cells including the stem cell, but it is primarily mode of action meaning it is working the most is on megakaryocytes progenitor cells and megakaryocytes. So, if you give a culture of bone marrow thrombopoietin that binds the receptor on megakaryocytes progenitor cells and makes them grow into megakaryocytes and may in turn make platelets.

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DR. BLUE:

So, is there a way to increase TPO production in the body?

DR. KUTER:

Well interesting enough the left thrombopoietin is made of a constant or constitute fashion of the body. Nothing we know so far can increase or decrease this production other than damage the liver where you would remove part of the liver. So, we cannot directly stimulate the body to make more thrombopoietin.

DR. BLUE:

This liver damage has had increase or decreased the amount of thrombopoietin it has made?

DR. KUTER:

Well transiently if you would just doing a highly damage the liver, a small amount will be released in circulation, but with liver damage such as cirrhosis, the production of thrombopoietin drops enormously and that is why most patient's with cirrhosis have diminished platelet counts.

DR. BLUE:

What are we doing to try and find a way to increase this TPO production in the body?

DR. KUTER:

Again, right now, there are many efforts to use other drugs to try to increase an endogenous thrombopoietin production. To-date nothing has been identified that increases your normal production of thrombopoietin, which is wide exogenous thrombopoietins that was made by the biotechnology industry have been very effective in this area.

DR. BLUE:

So, what TPO analogs have been developed and how did the first generation work?

DR. KUTER:

Well soon after with the cloning of thrombopoietin in 1994 to recombinant molecules and to the clinical trials, one was called recombinant human thrombopoietin, which was basically a molecular mimic of native molecule in present all of us. The other was a molecule called PEG-and MGDF which was a smaller protein coupled with polyethylene glycol, and both these molecules entered the very aggressive clinical trials in many areas back in 1995. To make a long story brief, these molecules were found to be effective in increasing the platelet count in patients who are getting routine chemotherapy such as that for lung cancer or ovarian cancer. They increase the platelet count in patients who were apheresis donors. These are people donating platelets to the blood bank. They help some patients with ITP help the platelet count rise and they also benefit a small group of patients with a thing called myelodysplastic syndrome. What was surprising is that molecules did not have any effect in the areas where platelets are commonly required for patient support such as acute myelogenous leukemia and bone marrow transplantation.

DR. BLUE:

And do you have any idea why they worked for some patients and not for others?

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DR. KUTER:

I suspect the major reason why they worked in some situations is the presence of a reasonably normal bone marrow and no things that suppressed the marrow. I think the reason that did not work in bone marrow transplantations because the levels of thrombopoietin in those individuals were already quite high because the liver was still making adequate amounts of thrombopoietin and probably secondly because the marrow do not have any bone marrow cells in it that could be acted upon by this hormone.

DR. BLUE:

And what are the next generations of TPO analogs and how are they different?

DR. KUTER:

Well again the reason the next generation analogs failed the test was not because of lack of efficacy. They failed because one of them, the PEG related MGDF molecule had antibodies develop against it. They cross-reacted with the native thrombopoietin present in all of us, and as I mentioned, a liver makes a constant amount of thrombopoietin every day. If an antibody occurs in our bodies and binds that thrombopoietin, we effectively knock out thrombopoietin production in a human and that is exactly what happened in 13 individuals in the clinical trial I held around back in the late 1990s. So, this led to an attempt by our very fertile minds in biotech to develop molecules that were not antigenic and get stimulated with the platelet count. So there have been several types of thrombopoietin what are called medics had been made. One of the medics based upon the protein structure of thrombopoietin these are peptides that bind the receptor, but do not have an amino acid sequence like that of thrombopoietin. These will activate the thrombopoietin receptor and in general turn it on and increase platelet production. Since peptides have a rather short half-life, they have been insinuated or inserted into other molecules such as IgG. They have given a longer half-life. In contrast, screens for small molecules, chemicals that stimulate platelet production and bind the receptor have been very good in identifying molecules that bind the thrombopoietin receptor and activate it and use of _____ chemicals, which are orally available you can be taken them by pill form rather than injection that increase the platelet count, and finally there have been several monoclonal antibodies that have been made to bind the receptor and activate it.

DR. BLUE:

I would like to thank our guest, Dr. David J. Kuter, Chief of Hematology at Massachusetts General Hospital in Boston and professor of medicine at Harvard Medical School for joining us to discuss the new generation of treatments for idiopathic thrombocytopenic purpura.

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