Thrombopoietin & Improved Platlet Disease Management

Platelets are critical to human survival. What is the cutting edge platelet research and what clinical impact is it having? Welcome to the clinicians roundtable. I am your host, Dr. Bruce Bloom and joining us to discuss breakthroughs in platelet research is Dr. David J. Kuter, Chief of Hematology at the Massachusetts General Hospital in Boston. Dr. Kuter is a board certified physician in Internal Medicine, Hematology, and Medical Oncology and he chairs the heparin-induced thrombocytopenia subcommittee of the NIH Network for Transfusion, Medicine, Hemostasis. He is also a professor of medicine at Harvard Medical School.

HOST:
Dr. Bruce Bloom.
DR. BRUCE BLOOM:
Dr. Kuter, welcome to ReachMD.

DR. DAVID KUTER:
Thank you, Dr. Bloom. It is a pleasure to be with you today to talk about these new areas.

DR. BRUCE BLOOM:
So when did the modern era of platelet research begin?

DR. DAVID KUTER:
It actually began very recently in 1994 when the molecule thrombopoietin was discovered.

DR. BRUCE BLOOM:
So newer data suggests that platelet diseases are both disorders of increased destruction and decreased production, how do we learn that?

DR. DAVID KUTER:
Again, primarily the condition called ITP or immune thrombocytopenic purpura. We have learnt from, what I call, a platelet kinetic studies that in patients with ITP, which has long been known to be associated with antibodies that bind platelets and destroy them, we have learnt from kinetic studies
recently that those patients who we would have thought would increase the rate of platelet production didn’t do so and hence most patients who have ITP or platelets have been destroyed, have a situation where their hope for compensation does not occur and most patients with ITP have a normal or only slight increased rate of platelet production.

**DR. BRUCE BLOOM:**

What’s the molecule that regulates all this and what have learnt about it recently?

**DR. DAVID KUTER:**
The molecule that has set us in a different track since 1994 was the discovery of thrombopoietin. Thrombopoietin is a 94,000 molecular weight protein, which is made in the liver. It is made in the constant fashion and it enters our circulations and it binds the target receptors called the thrombopoietin receptor and bone marrow cells and that it promotes the growth of the precursor cell megakaryocytes, which in turn make platelets.

**DR. BRUCE BLOOM:**

So why don’t we just find ways to increase the production of thrombopoietin inside the body?

**DR. DAVID KUTER:**

Well, interestingly enough, the only hematopoietic growth factor, which actually is regulated in our body in such a fashion is erythropoietin. When we are anemic, we make more erythropoietin, but all the other hematopoietic growth factors such as granulocyte colony stimulating factor, monocyte colony stimulating factor – now thrombopoietin, are regulated in a much different fashion. They are all made in a constant rate in our body, thrombopoietin being made in a constant rate by the liver and nothing
increases or decreases the rate of production. The only exceptional make is if you have liver disease and your liver is destroyed or partially destroyed say by cirrhosis, your production of thrombopoietin drops dramatically and your platelet count also drops.

DR. BRUCE BLOOM:
Can we think of an evolutionary reason why thrombopoietin would be regulated in this way?

DR. DAVID KUTER:
I wish I could, I have been thinking about this for a number of years. What I will tell you is in situations or animals where we knock out the productional thrombopoietin, the platelet count drops down to a low level, but not a level that is incompatible with life. So you can have animals and also humans that have platelet counts about 1/10th of normal, which is what happens when you don't have thrombopoietin and these animals live totally well. I suspect as we evolved as a fighting society and blood a lot, a higher platelet count might have been more protective, but I can't give you a good answer for that.

DR. BRUCE BLOOM:
Are there other animal species that have a different kind of thrombopoietin regulation?

DR. DAVID KUTER:
No, well, we have evolved almost all vertebrate species to have platelets regulated in this fashion.
DR. BRUCE BLOOM:
So have we made an analogue of thrombopoietin and how does it work?

DR. DAVID KUTER:
Yes, as soon as thrombopoietin was identified back in 1994, within a year, 2 recombinant thrombopoietins were identified and they entered clinical practice; one was a virtual replica of the endogenous native thrombopoietin and the other was a portion of molecule that bound the receptor only that was coupled to polyethylene glycol called PEG, anti-Tf and both of these had half lives in a circulation of 40 hours, both rapidly made the platelet count rise in animals and in humans who were human volunteers and they were tested in a wide variety of situations.

DR. BRUCE BLOOM:
And are either one of those down in the market and are they working right now?

DR. DAVID KUTER:
No, despite the fact that they showed a benefit in a number of areas and in brief areas that they showed benefit in was chemotherapy-induced thrombocytopenia, platelet apheresis donors, and a few patients with ITP, they are not in the market now because one of the drug had antibodies developed against it, the PEG imaged F molecule. What happened is those antibodies bound the recombinant product, but then also cross reacted with the native molecule and since we make the native molecule with constant rate, we effectively knocked out production of thrombopoietin. So these early experiments that were done that show benefit from thrombopoietin were stopped about 1998 or up to 2000 because of the antibody issue.
DR. BRUCE BLOOM:
And has the scientific community made different kinds of new analogues and how are they working?

DR. DAVID KUTER:
Yes, because of the benefit that we saw with the early molecules, we felt that we could make a non-immunogenic molecule that would have clinical benefit and this also allowed chemists and scientists to develop different kinds of thrombopoietic molecules. One type was to make a peptide, which was activating the thrombopoietin receptor, but did not have the same amino acid sequences to the native molecule. Hence if an antibody was made against this new peptide, it would not cross react and knock out the endogenous thrombopoietin production and several such peptides were made. They were then inserted in a different carrier molecule to prolong the half life and one of these called romiplostim is currently FDA approved for the treatment of ITP. Other areas of investigation identified small chemicals, which are not orally available that bound the thrombopoietin receptor and activated it and these molecules are in clinical development right now and finally you can make monoclonal antibodies that bind the thrombopoietin receptor and activate it and increase the platelet count and these are also being developed at a much slower rate by several pharmaceutical companies.

DR. BRUCE BLOOM:
You mentioned that romiplostim is on the market now. When was it approved and when do you think it will get wide scale use?

DR. DAVID KUTER:
Romiplostim was approved in August of 2008; it is a molecule which was studied primarily in ITP and it is currently approved for ITP. The brand name is Nplate and the generic name is romiplostim. It was developed under the name AMG 531. It is a molecule, which showed major benefit in treating ITP patients with more than 88% of patients responding to it in the clinical trial that lasted for 24 weeks.
This molecule is now available and is being used by practitioners to treat patients with refractory ITP currently.

**DR. BRUCE BLOOM:**

And did it work for both splenectomized and non-splenectomized patients?

**DR. DAVID KUTER:**

Yes, that’s what is striking about this molecule. It worked almost as well in splenectomized patients who had received up to 6 prior treatment regimens and failed them as they did in patients who did not get them splenectomized with response rates being about 78% in the splenectomized group and 88% in those who had not yet been splenectomized. The response rates also lasted for a long time. In patients on our 24-week trial, most patients maintained a platelet count, which previously had been below 30,000 and was now above 50,000 most of the time. In open label studies, which followed those initial phase 3 studies, we have had patients now out on these molecules for 3 or 4 years with stable control over platelet count over 80% of the time, so these molecules work in a short period of time over 24 weeks on 1 clinical trial and now on a very long open label trial, they have been showing efficacy to 156 months.

**DR. BRUCE BLOOM:**

What else has this drug done for patients with ITP besides increased their platelet counts?

**DR. DAVID KUTER:**

There are many things that ITP patients want? One of their concern is about a higher platelet count and as I mentioned this drug increased the platelet count and quite dramatically maintained it. The second
thing ITP patients want to do is come off their concomitant therapies such as steroids and immunosuppressive agents and it was dramatic about our study is that in the splenectomized group, for example, a 100% of patients who have been on steroids either discontinued or reduced their steroid dose versus only 17% of patients who are in the placebo group of patients. Furthermore the patients with ITP tend to have their platelet counts wax and wane, they rise and fall from time to time and patients require what are called rescue medications; things like IVIG and anti-D that transiently increase the platelet count and the use of such rescue medications dropped dramatically by almost two-thirds in patients who received the romiplostim drug versus those who received placebo.

DR. BRUCE BLOOM:

It is the only reason for us to believe that this will not be durable for these patients?

DR. DAVID KUTER:

I think right now in the studies we have done with patients now 3 or 4 years in these molecules, there has been no suggestion of tachyphylaxis or loss of response. There had been a few long-term potential risks identified and those are being monitored very closely in our ongoing clinical trials.

DR. BRUCE BLOOM:

And what are those side effects and what are the less severe ones that patients experience as well?

DR. DAVID KUTER:

From romiplostim, the major minor side effect is this is a subcutaneous injection usually given once a week and most patients have no trouble with this. It certainly pales in comparison to getting prednisone everyday at rather toxic doses. Many patients, perhaps a third had a mild headache within several
hours of receiving administration and those of the two minor side effects had occurred. Another issue that did appear on our clinical trials particularly when we stopped the drug is this is a therapy that boosts the platelet production, but does not affect the concurrent platelet destruction, so as soon as you stop stimulating platelet production, the platelet count falls and in about a 4 of 56 patients in one study, the platelet count actually fell below their prior baseline and it took a couple of weeks for it to return back to their prior baseline. This did not result in any bad clinical sequelae, but stopping these molecules in ITP is not a wise idea, at least doing abruptly. Another concern, which came out of our clinical trials is the occurrence of what is called reticulin in the bone marrow. Now reticulin, which is a type of collagen that is identified by a silver staining technique, which was created 100 years ago, actually is present in two-thirds of normal individuals. In ITP patients, it is probably present to the same extent. In 10 out of over 200 patients, we have studied this reticulin appeared to be increasing a bit in some of these patients. It did not appear to cause them to have any hematologic abnormalities, but again it is something, which we are studying right now to see if there is any long-term sequelae of reticulin formation. Why might this be of concern, it is of concern because many physicians associate reticulin formation with a clonal bone marrow disease called myelofibrosis and I think what’s probably important to state right now is the administration of this class of drugs to ITP patients does not appear to cause the disease myelofibrosis, but simply an increase in reticulin, which is reversible.

DR. BRUCE BLOOM:

Can these treatments that are now being used for ITP be used in any other platelet disorders like myelodysplastic syndrome or thrombocytopenia due to hepatitis C?

DR. DAVID KUTER:

Yes, and I think this is where a lot of great excitement occurs right now. I think that in MDS patients, a small trial done at the M.D. Anderson Hospital and elsewhere showed that about half of patients who received romiplostim for a month had their platelet count rise above 50,000. This did not seem to have any effect upon bleeding risks, but the major concern that was found in most studies was some patients had increase in blast percentage, which has given us some pause in these studies. There are ongoing studies that are just about to be started as well looking at the use of romiplostim in MDS
patients who are getting concurrent chemotherapy. I think the major area for these drugs might be in hepatitis C thrombocytopenia as you know hepatitis C is a very common condition in our country, thrombocytopenia also commonly ensues and if the platelet count is less than 70,000 in some of these individuals, anti-retroviral therapy which may be curative to hepatitis C is often not given or at least complicated by the thrombocytopenia and using a different thrombopoietic agent called eltrombopag, which is a small molecule, distinct in structure and different from romiplostim, it was shown in a very nice clinical trial that platelet counts could be brought into the normal range with oral administration of this drug, eltrombopag and the patients then could undertake and successfully complete antiretroviral therapy over the next 12 weeks.

DR. BRUCE BLOOM:

I would like to thank our guest, Dr. David J. Kuter, Chief of Hematology at the Massachusetts General Hospital in Boston and Professor of Medicine at the Harvard Medical School, for joining us to discuss breakthroughs in platelet research. You have been listening to the clinicians roundtable on ReachMD, a channel for medical professionals. For a complete program guide and podcast, visit www.reachmd.com and thank you for listening.

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