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Optimizing Erythropoietic Therapy for CKD

ERYTHROPOIETIC STIMULATING AGENTS, HOW CAN THEY BEST HELP PATIENTS WITH CHRONIC KIDNEY DISEASE

Erythropoietic stimulating agents, how can they best help patients with chronic kidney disease. You are listening to ReachMD, The Channel For Medical Professionals. Welcome to Focus on Pharmacy. I am your host, Dr. Charles Turck, PharmD. Our guest is Dr. Sarah Tomasello, PharmD, Clinical Associate Professor at the Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey and a clinical specialist in nephrology at Robert Wood Johnson University Hospital in New Brunswick, New Jersey.

DR. CHARLES TURCK:

Dr. Tomasello welcome to the program.

DR. SARAH TOMASELLO:

Thank you, thank you very much for having me, I am excited about this.

DR. CHARLES TURCK:

Lets start out with some context. Why do erythropoietic-stimulating agents or ESAs matter? Who exactly do they help?

DR. SARAH TOMASELLO:

ESA products are indicated for a variety of different types of anemia, but particularly for anemia of chronic kidney disease because the kidneys are responsible for producing the hormone erythropoietin and as kidney function declines, the body is less able to produce this hormone and the need for exogenous hormone is evident. So although we can use ESAs in other disease state to help with anemia, kidney disease particularly rely on the exogenous epoetin alpha or darbepoetin or whatever agent we are using.

DR. CHARLES TURCK:

How many patients in the US are impacted by ESAs?

DR. SARAH TOMASELLO:

Well the more recent prevalence data suggests that there is about 20 million patients in the United States with some degree of chronic kidney disease. The patients may develop anemia even in the most mild stages of kidney disease which we would call stage 1 and stage 2, but usually it is only a small percentage of patients what would be affected at that stage. The biggest burden is the patients with more severe kidney disease and that is estimated to be approximately 8 million people with stage III, IV, or V which is the end-stage kidney disease.

DR. CHARLES TURCK:

Just to continue to define the scope of the problem. What are some of the long-term complications of anemia in patients with chronic kidney disease?

DR. SARAH TOMASELLO:

The most glaring would be probably in the area of quality of life as well as increased risk for cardiovascular morbidity, mortality. Anemia can effect every body system including cognition and exercise tolerance and cause a lot of fatigue and decrease quality of life. Also anemia puts a tremendous strain on the heart to work harder to profuse the body with oxygen. So if you think about it as a patient is becoming more and more anemic, the heart will try to compensate for the decreased oxygenation capacity and will start to work harder to pump more blood causing eventually left ventricular hypertrophy and potentially chronic heart disease in some patients. So it is well known that patients with chronic kidney disease and anemia are at a higher risk of cardiovascular morbidity, mortality and in fact, that is the number one cause of death in patients who do live through dialysis which is end-stage kidney disease.

DR. CHARLES TURCK:

So ESAs were introduced to the US market really just in the last few decades. How was anemia of chronic kidney disease treated before their advent?

DR. SARAH TOMASELLO:

The contrast is amazing. It is like night and day. The first commercially available erythropoietic agent was epoetin alpha in this country in 1989 and before that patients really were treated with transfusions on red blood cells as well as androgen therapy using agents like testosterone or fluoxymestrone to enhance erythropoiesis. Unfortunately, the side effects of those agents were pretty severe and the scarcity of blood and infectious complications as well as the risk of exposing patients to different antigens from the transfusions would possibly preclude them from transplant later on. So it was really kind of a nightmare.

DR. CHARLES TURCK:

How important is it for clinicians to ensure that patients have repleted iron stores before starting ESA therapy.

DR. SARAH TOMASELLO:

It is essential. I would like an ESAs and iron to how your car works. If you think about a car, you have gas in the gas tank or in this model we would have iron in the gas tank and ESAs are like putting our foot down on the gas pedal to speed up erythropoiesis and go forward. If you run out of gas in the gas tank, it doesn't matter how much you are stepping on the accelerator. You are not going to go anywhere. Certainly, patients can still maintain some amount of erythropoiesis with a minimal amount of iron, but if we really wanted to optimize our ESA use and optimize erythropoiesis, we want to make sure that the iron is available to the bone marrow and the iron stores are also repleted.

DR. CHARLES TURCK:

So what sort of targets from an iron study's perspective should clinicians be looking to hit, if we are starting ESA therapy.

DR. SARAH TOMASELLO:

The National Kidney Foundation KDOQI guidelines recommend that the 2 parameters that are most important would be the TSAT which is the transferrin saturation percent which is a marker of the iron that is available to the bone marrow to be used readily for erythropoiesis and the ferritin which is a marker not all that great marker, but it is a marker of our stored iron. The iron that is sequestered in the reticula endothelial system waiting to be mobilized and used if necessary. KDOQI recommends that the TSAT be maintained between 20 to 50% and for patients who are not yet on hemodialysis, the ferritin should be greater than 100 ng/mL and the patients who are on hemodialysis, the ferritin should be greater than 200 ng/mL and this is because patients on hemodialysis are losing blood every single time they have a dialysis session. Some blood is lost in the tubing or microthrombi, so the stores should be kept a little bit higher in those situations.

DR. CHARLES TURCK:

If you are just joining us, you are listening to Focus on Pharmacy. I am your host, Dr. Charles Turck. Our guest is Dr. Sara Tomasello, Clinical Associate Professor of the Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey and a clinical specialist in nephrology at Robert Wood Johnson University Hospital in New Brunswick, New Jersey. We are discussing the role of erythropoietic stimulating agents or ESAs in anemia of chronic kidney disease.

Dr. Tomasello are there any barriers to the accurate interpretation of iron studies in the setting of ESA management in chronic kidney disease?

DR. SARAH TOMASELLO:

Definitely, it is not an exact science. At this point, we do use the transferrin saturation percent as I mentioned. Additionally the KDOQI guidelines suggest using the hemoglobin content of reticulocytes or the CHR as a better measure of actually how much iron is going into each new baby red blood cell at the bone marrow. Unfortunately not all institutions have these laboratory parameters available to them, so we may be still using the TSAT instead of the CHR. The other problem is the ferritin. Ferritin is a protein that may or may not bind to iron and is also an acute phase reactant. So in a situation of inflammation or infection, ferritin is dumped into the serum in response to this insult to the body and when you measure the serum ferritin concentration, it may appear that you have tons of ferritin in the serum, however, that ferritin is not indicative of the stored iron that is in the reticula endothelial system, it is only a measure of the ferritin that happens to be in the serum at that moment. So it can be very misleading and typically when we are talking about the evaluation of iron studies, we must take into account the clinical picture is the patient infected, do they have some source of chronic inflammation that is causing their ferritin levels to be high and that would suggest it may not be an indication of our iron stores, but rather an acute process.

DR. CHARLES TURCK:

What are some other considerations that clinicians might want to keep in mind when choosing a product for iron supplementation or repletion? Are there any products in particular that you prefer over others in getting patients to their goal TSAT levels?

DR. SARAH TOMASELLO:

When using the intravenous iron preparation, those are the preferred preparations for patients on hemodialysis as we have consistent intravenous access to give those agents. With the IV products, there are the older products, iron dextran which is name brand either Dexferrum or INFeD and then we have 2 newer products the iron sucrose or sodium ferric gluconate. The 2 older products that are iron dextran products have been associated with an increased risk of anaphylactoid reactions or anaphylactic reactions and for some time now have on to disuse because of the newer agents. They may still be acceptable agents to use in certain circumstances; however, I think many institutions have chosen the newer agents due to the decreased risk of these adverse events. It is important with any of these agents, they have certain infusion-related reactions if they are instilled too quickly, so instilling them over a good amount of time may decrease the adverse reactions and in general the 2 newer agents that I mentioned, iron sucrose and sodium ferric gluconate are very well tolerated. There is concern that some of the intravenous iron products may cause an inflammatory reaction and accelerate processes like atherosclerosis. This is an area that is receiving a lot of attention; a lot of research is being done to gain more knowledge about this possibility, so I think we will hearing more about that in the near future.

DR. CHARLES TURCK:

How often should iron studies be monitored while the patient is on ESAs?

DR. SARAH TOMASELLO:

The KDOQI guidelines recommend that for patients who are receiving ESA therapy, if they are chronic hemodialysis patients, but not yet on hemodialysis, the iron studies should be monitored quarterly. If they are stable although there may be situations where more frequent monitoring would be prudent situation where the hemoglobin is decreasing without an obvious cause or dose change of the erythropoietic agents. For patients on hemodialysis, generally speaking again probably more frequent monitoring is necessary if their hemoglobins are not stable and otherwise we can monitor them every 3 months.

DR. CHARLES TURCK:

Now drawing upon your experience, how is it that you most commonly see ESAs misused in clinical practice, is there anything that clinicians tend to forget or fail to take into account when ordering or prescribing ESA therapy.

DR. SARAH TOMASELLO:

In my practice, because I work at an acute care facility, I see a lot of very sick patients who have a lot of reasons to be anemic besides just chronic kidney disease. They may have blood loss from gastrointestinal bleeding. They may have frequent phlebotomy because they are acutely ill. So in my practice what I encounter a lot is escalating doses of ESA without necessarily working up any other causes of the anemia and trying to correct any modifiable causes of anemia. So for instance increasing the dose of the ESA without obtaining

iron studies or increasing the dose of ESAs without seeing if the patient has B12 or folate deficiency. I think that is probably the most common problem in my practice, it is just escalating doses without necessarily trying anything else.

DR. CHARLES TURCK:

We have been speaking with Dr. Sarah Tomasello about the role of ESAs and anemia of chronic kidney disease. Dr. Tomasello thank you so much for joining us.

DR. SARAH TOMASELLO:

Thank you very much.

DR. CHARLES TURCK:

I am Dr. Charles Turck; you have been listening to Focus on Pharmacy on ReachMD, The Channel for Medical Professionals. Be sure to visit our web site at www.reachMD.com featuring on-demand pod casts of our entire library and thank you for listening.