UNITED STATES FOOD AND DRUG ADMINISTRATION

PUBLIC WORKSHOP

SCIENTIFIC EVIDENCE IN DEVELOPMENT OF HCT/Ps SUBJECT TO PREMARKET APPROVAL

Silver Spring, Maryland

Thursday, September 8, 2016

marrow cell transplant experiments but they have been under the oversight of the FDA. We are aware that some of the procedures that have been out there have had complications and I believe you may hear about them soon and we advocate that all of the therapy should have (inaudible) data and have that regulatory oversight. Again, we do not advocate the use of pay policy for these sort of studies.

DR. KAHN: Thank you Dr. Mansfield. Our next speaker is Thomas Albini. Dr. Albini is an Associate Professor of Clinical Ophthalmology at the Bask and Palmer Eye Institute in Miami.

DR. ALBINI: Thank you very much for the invitation to speak here. Thanks to the FDA and Dr. Kahn and it is also a pleasure to be following after Dr. Mansfield and my colleagues at Baskin Palmer Eye Institute and myself have been familiar with Foundation for Fighting Blindness. I've worked with them for years and I have to say I have very little of substance of what he said from the patient's perspective. I think it is a great

organization in really helping patients who have these blinding conditions. But what I'm going to share with you is what I think is a very rare instance of a dreadful outcome from a "health provider" in South Florida where I think there was really demonstrated neglect for both patient safety and for any sort of scientific integrity from what was being done. Just to discuss a real case scenario with three patients who were treated, came from elsewhere in the country, were treated in South Florida and then were seen at my facility within two or three days after the treatment because of complications and of note this happened three times not just once. It was really a very horrifying situation. I have no relevant disclosures.

We've heard already about macular degeneration this morning and a little bit in the last talk and its important to say that for most patients with macular degeneration they preserve their vision for quite a long time. Dry macular degeneration especially in its early

manifestations is really consistent with retained vision for decades for the vast majority of patients. But for about 10 percent of the patients they will go on to develop one of the severe forms. There is the wet form of macular degeneration. This is the form where patients are routinely getting monthly injections of various biologic agents to control the fluid that accumulates underneath the retina within the retina and causes vision loss. Another 10 percent of the macular degeneration patients will develop severe dry form macular degeneration where there is atrophy of the retinal pigment epithelium as we discussed earlier this morning.

Now these patients will go on to severe vision loss for the vast majority of them if left untreated. We have very good treatment now for the wet form. For the dry form we still don't have a very good treatment. So the story is the patient moves to Florida and is getting excited about taking up golf as their main retirement activity and then loses the ability to drive, read

and recognize faces. These patients maintain good peripheral vision so they can get around a room but they lose their central vision.

So the wet macular degeneration outcomes these are outcomes from pivotal trials for a drug called Ramibizumab that was introduced by Genentech back in 2006 and really have shown marked improvement of visual acuity from baseline whereas in the control groups the patients lost visual acuity. This is maintained out at least through the first three or four years, we've got data through seven years. You lose a little bit of vision but if you continue with these monthly injections of biologics you can really maintain that visual acuity for a long time.

In dry macular degeneration the number of different strategies that are out there trying to find a treatment including biologics, small molecules, gene therapies and cell therapies as we're talking about here today. Perhaps these embryonic stem cell derived retinal pigment epithelial cells much like the cells that were

discussed earlier today. But provided from another source a company called Ocata Therapeutics that published their results in The Lancet, this is for dry macular degeneration and really showed some modest but apparently real visual acuity gains and some other biologic findings on various imaging studies demonstrating that these cells actually took residence and where the retinal pigment epithelium should be in the sub-retinal space and had some demonstrated function as well in that space. So we are having some victories in this field. They are coming slowly but I think this is very welcome news that there is some real data that stem cells are working for dry macular degeneration.

Now one of the delivery methods that we haven't talked about today is just intravitreal delivery which is perhaps the simplest form of delivery. It is the form of delivery that we use for intravitreal injections of biologics for wet macular degeneration like that drug Ramibizumab that I just mentioned. In this case these four

different trials that are listed on clinicaltrials.gov are looking at taking stem cells and delivering them straight into the vitreous cavity. One of these studies was using adipose derived stem cells where the adipose tissue was harvested on the same day that the intravitreal injection was done and was then processed in a very quick fashion under an hour. In the same procedure injected them bilaterally into both eyes. It is the outcome of this procedure that I'm going to be talking about. This company that was doing this unbelievably without an ophthalmologist directly involved in what was happening without and M.D. injecting the cells. They were injected by a nurse practitioner without M.D. oversight. This has resulted in really bad outcomes and as I said again demonstrated a complete lack of regard to the patient safety and to any sort of scientific integrity. They did have a trial that was posted on clinicaltrials.gov. The patients when I saw them and they came to the hospital a day or two

after this happened, by the way this was a very painful procedure for them which is not typical for injections. They are usually somewhat painful but not the type of profound paint that these patients were describing. They were under the impression that they had participated in a clinical trial. When we finally were able to see the informed consents that the patients had signed the informed consents actually weren't for any clinical trial they were just for a basically fee for service procedure which was explained to the patient to have the possibility of resulting in blindness and that it was outside the standard of care of treatment. That's how this particular set of injections was performed.

So we're reporting here three cases of bilateral vision loss after bilateral intravitreal injection of stem cells in a stem cell clinic. All patients underwent intravitreal injections of the usual dose of volume that is injected with autologous adipose tissue derived stem cells. All three of the patients paid $5000 for the

procedures. One of the patients also had the same stem cell preparation injected into both of her knees on the same day for an extra $1200. They signed a consent form for the procedure but not a study consent and all three of the patients here had seen the clinicaltrials.gov website. One of the patients, the first patient I'll describe was a statistician who had been involved in clinical research and these patients were under the impression that the clinicaltrials.gov website lended some credibility to the study.

The first patient is a 72-year-old female with a history of dry macular degeneration and vision of 20/60 and 20/40 which is pretty good vision. 20/40 is good enough to drive if that were your only eye at least in the State of Florida and it is good enough to read standard newspaper print. This is not perfect vision but it is very functional vision. She came in with three days of decreased vision, pain and vomiting and nausea. Visual acuity on presentation was hand motions only, she couldn't see the large E on

the eye chart out of either of her eyes and she had extremely high intraocular pressures. What we found in this particular patient these are ultrasounds showing anterior displacement of the crystalline lens which the zonules that hold the lens in place apparently became loose somehow. This is probably not because of the needle or a direct pushing or ripping of the lens but we think it is an enzymatic digestion that something that was injected into the eye. Trypsin for example is known to digest the zonules and used to be part of standard intracapsular cataract surgery. It is a way to remove the lens. But some protein that was injected in the eye probably dislodged these lenses that pushed forward that causes the obstruction of outflow of fluid from the eye, increases the pressures in the eye which of course is bad for the optic nerve that causes an acute glaucoma. She was found to have a vitreous hemorrhage in both eyes there was no view to the back. We had to remove the lens emergently, remove the vitreous that was in the back of the

eye and remove the blood that was there. She was found to have a retinal detachment in the right eye and over one week her vision dropped down to no light perception in either eye. She ultimately had retinal detachments in both eyes that needed to be fixed. Here you see a lot of intraretinal hemorrhage all throughout the fundus, retinal detachment, displaced lenses, really a disastrous outcome that you never see after routine injection of biologics for wet macular degeneration.

The second patient is a 78-year-old female. She had wet macular degeneration which was well controlled. She hadn't required an anti veg-F injection for two years prior to undergoing this therapy. Her visual acuity in the right eye had just dropped to a point where she was losing her driver's license and therefore sought out this treatment as a potential remedy for herself that her daughter found on the web. Again, from the web was referenced to the clinicaltrials.gov website and mentioned that when we spoke to her. She was also under the impression that she was

participating in a clinical trial. Similar diffuse hemorrhage in both eyes worse on the left than right. She presented without retinal detachments. Also very bad vision, counting fingers again not formed vision in either eye. She was initially observed and eventually developed retinal detachments in both eyes requiring treatment and now at least has one eye with visual acuity of 20/200 and the other one doesn't have any formed vision.

This is the third patient 88-year-old female, dry macular degeneration. Had a visual acuity of 20/40 again relatively good vision in the right, 20/200 in the left eye prior to injection. She came in seven days after the procedure with light perception vision only in the right eye, 20/200 in the left eye. A very mature looking retinal detachment with what we call PVR, Proliferative Vitreal Retinopathy which one of the reasons the retinal detachment surgery fails is that you get a growth of scar tissue on the surface of the retina fibroblast that contract and

pull the retina back off of the wall of the eye. It is possible that the stem cells which in some of the imaging that we have seen to take residence on the anterior surface of the retina and they may be actually pulling the retina off and being the reason why all these patients eventually developed retinal detachments in both eyes as this patient did in her left eye about a month later.

So these were the initial vision of the patients ranging from 20/40 to 20/200. Their presenting visual acuity when they came to the clinic ranging from 20/200 to light perception. Five of the eyes had lens subluxation, some were along their course. Four eyes had severe intraretinal hemorrhages. All of the eyes eventually developed retinal detachment and the ultimate visual acuity was legal blindness in all three of these ladies. We had a one year follow up and unfortunately none of the patients have gotten any better.

So what are the potential causes for these findings? Well they include contamination

of stem cell with toxic substances during preparation. Use of trypsin or collagenase during stem cell isolation which we're looking at because of that zonular weakness that we've seen and maybe it is not appropriately washed out. And there may be some genuine affect from growth factors in cytokines and the vitreous and blood derived undifferentiated stem cells to myofibroblast cells resulting in detachment of the surface of the retina. There is some biologic effect of these cells and some of the phase one studies have also been stopped because of retinal detachment where there has been inadvertent seepage of cells that were injected into the subretinal space coming back into the vitreous cavity and then retinal detachment was seen in a lot of those. So there may be some danger from this mode of delivery. There is real science being done on intravitreal injection of stem cells so I certainly don't want to put any hindrance to that. There may be a good way to deliver intravitreally but we hypothesize that intravitreal delivery at least in these cases

may have caused some of the problems.

The patients were referred to clinicaltrials.gov which listed an IRB approved study however the patients were not enrolled in the study. Injections were being performed without FDA oversight. There was no IND obtained by this clinic. These were patient funded research procedures and we've talked about the dangers of that. Unbelievably, an American licensed physician was not involved in the care and the injections were performed by a nurse practitioner.

Sorry to share this with you but I think it is an important thing for patients to know and as I've learned today the extent of the industry that is around these unregulated stem cell clinics I hope we don't see more of this with intraocular delivery. Thank you.

DR. KAHN: Thank you. Our last speaker for this session before the panel is Dr. Michael Miller. Dr. Miller is a Senior Clinical Fellow in neuropathology at the Brigham and Women's Hospital

wondering if we saw that result with the collagenase. In the case where we saw that result with collagenase have we seen that collagenase in other labs and when we talk about the training I know that that group has a training operation. I've come in and found various discrepancies. So when I think about taking collagenase away from the field I think that there needs to be better training. Maybe we could form some kind of training system.

DR. ALBINI: I can't speak to the enzymes but what I can speak to is that as a retina surgeon I don't think that my colleagues were aware this was going on. This was sort of off the map. So in terms of what we're training retina specialists I think the answer is nothing because I think there just wasn't awareness of this. When I've presented these cases at retina meetings everybody has been in shock and is unaware of other problems or that clinics like this even exist or what the market place is for stem cell clinics and so forth. So that's not out

there and the only thing I can say is that I do think probably a minority of retina specialists would recommend to their patients to try something like this. I can imagine I don't know how small the minority is but I can imagine and I think I've heard of some physicians who have recommended to patients where there are no other options why don't you try this -- not the particular one that I discussed but why don't you try some sort of stem cell therapy. I think that just comes out of the fact because we as retina specialists don't really talk about any of this. So I've learned a lot today and I think there probably should be a mechanism that some of what I've seen here today be communicated back to my colleagues.

DR. KAHN: Okay really, really, last, do you want to say something?

DR. KIMMELMAN: I just want to say two things about this. So first of all, I'm not a physician, I don't dispense medical advice but it seems to me that physicians dread having to tell patients that their options are incredibly thin