FDA Media Teleconference on TNF Inhibitors
Tumor Necrosis factor-α blockers

Moderator: Susan Cruzan
September 4, 2008
10:45 am ET

Coordinator: Welcome and thank you for standing by. All participants are in a listen only mode until the question and answer session. If you'd like to ask a question please press star 1.

Today's conference is being recorded, if you have any objections you may disconnect at this time. I would now like to turn the call over to Miss Susan Cruzan, ma'am you may begin.

Susan Cruzan: Thank you so much and good morning everyone and welcome. I am Susan Cruzan with FDA's Office of Public Affairs. Today we will discuss FDA's safety announcement related to four drugs known as TNF blockers.

The CDER information is posted on CDER's website under News From CDER. We also issued a posted press release on fda.gov. Joining us today are several experts from the Center for Drug Evaluation and Research.

Our speaker today is Dr. Jeffrey Siegel, a clinical team leader in anesthesia, analgesia and rheumatology products. Also joining us are (Elan Chen) standing in for Dr. Joyce Korvick with the division of gastroenterology products and Dr. Elizabeth O'Shaughnessy who is a Medical Officer in the Division of Special Pathogens and Transplant Products.

We also have other CDER experts available to answer questions as needed. Dr. Siegel will now provide brief remarks and then we will open up the call for credentialed media only. Thank you, Dr. Siegel.

Jeffrey Siegel: Thank you Susan. Good morning and welcome. Great to have the opportunity to speak with you all today. We are presenting an important drug safety message that we hope that you will communicate to the public so we can increase awareness of these concerns associated with TNF blockers that are used for a variety of disease conditions.

Let me begin with a summary of FDA's actions relating to these TNF blockers. The Food and Drug Administration has asked the manufacturers of these four drug products, they include Enbrel, Remicade, Humira and Cimzia to highlight existing warnings for the development of fungal infections including histoplasmosis in particular.

The box warning which is the most serious warning in labeling must be upgraded to strongly warn doctors to consider the occurrence of histoplasmosis infection and other fungal infections in patients who develop serious illnesses that prove difficult to diagnose or who develop serious infections that are not responding to the current antibiotic treatment they are receiving.

We are taking this action under the FDA's new authorities under the FDAAA legislation. These infections need to be identified early enough so that treatment is not delayed.

We reviewed a number of cases where prognosis of histoplasmosis and these other fungal infections were delayed and this resulted in prolonged hospitalization and death in a number of cases.

To place this into perspective, although the development of these infections is uncommon, these drugs are widely used for a variety of disease conditions and these conditions vary product to product.

The conditions include rheumatoid arthritis, which is probably the most common use, but also they are used for Crohn's disease, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis.

Let me just go over a couple of areas that played a role in the taking announcement we're making today. So what did we take into account in making this new safety statement?

First these products are known to be an immunosuppressant and as I mentioned before they are used to treat a range of different diseases.

Our warning follows the recent review of adverse events that identified histoplasmosis and other fungal infections related to the use of these products.

We became aware of a case of an individual who was taking one of these products who died of histoplasmosis. Looking over the details of her case, it became apparent that she had a prolonged condition that was not diagnosed as histoplasmosis for a prolonged time.

And she eventually died of histoplasmosis. This case led us to become concerned that there might be other situations where physicians might not recognize histoplasmosis as the cause of the serious condition.

So therefore we reviewed our safety database and found 240 reports of histoplasmosis. Of these 240 cases, review of 21 of the cases showed that the histoplasmosis was not initially recognized.

And this was a prolonged hospitalization and death in some cases. So what is histoplasmosis? Histoplasmosis is a respiratory illness that has symptoms that are similar to influenza or the flu.

It's endemic in the Mississippi and Ohio River Valleys in the United States, endemic meaning that the fungus is more common there, and infection is much more common in those areas.

So what actions are we taking to address this problem? We are instructing the companies to change the warnings on their labels. These actions are good use of the FDA's new authority to alert the public the information for patients that the patients can use to promote more safe use of drug products.

What are the actions that we're asking to be taken? We're asking healthcare providers to be more vigilant in looking out for possible signs and symptoms of histoplasmosis and other fungal infections.

We're advising healthcare professionals to learn about the signs and symptoms and to educate their patients.

We're asking patients who reside or travel to regions where these fungal infections are endemic to suspect or consider an infection if they develop a serious fever or systemic illness.

And it's important for patients to also tell their health care provider if they are taking these TNF blocker medications so that they can help make appropriate decisions about treatment with anti-fungal therapy.

So what are these symptoms and infections with histoplasmosis? Patients on these drugs may have a serious fungal infection if they present with the following symptoms; fever, cough, unexplained weight loss, shortness of breath and fatigue. And if they do develop these signs and symptoms, they should promptly seek medical attention.

So what we're trying to do here is to help patients own their own healthcare. And our advice to patients is don't hesitate to contact your doctor if you see these key signs and symptoms that are related to these types of infections.

Our advice to healthcare providers is to maintain a high index of suspicion for histoplasmosis and other fungal infections in patients who develop signs and symptoms that have these characteristics considering patients who are a particular risk of developing these infections.

We think that healthcare providers in this situation should work with infectious disease specialists to figure out what the right course of action is to provide a definite diagnosis and to begin prompt treatment.

And finally in selected cases of patients who are at risk, doctors may want to begin treating their patients with what we call empiric antifungal therapy. This would be therapy based on the likelihood that a patient has histoplasmosis even before test results provide definitive proof, especially if they are patients with an endemic area or have traveled to an endemic area.

I think we'll stop here and I'll turn the call back to Susan. Thank you.

Susan Cruzan: Thank you Dr. Siegel. We can start the Q&A session now. I do want to remind reporters that we will allow one question with one follow up so that we can address everyone's questions.

And if you have additional questions you are welcome to email me, Susan Cruzan or Rita Chappelle in the Office of Public Affairs and we will work with our folks to get you the answers.

Again this is for credentialed media and we would like to take our first question. Thank you (Kelly).

Coordinator: If you'd like to ask a question please press star 1. To withdraw your question press star 2. One moment please.

Susan Cruzan: (Kelly), do we have any questions in the queue?

Coordinator: Yes. One moment. Okay, our first question comes from Carl Sears with NBC News, your line is open.

Carl Sears: Yes, how do these drugs cause these infections and are the companies cooperating fully with your findings?

Jeffrey Siegel: These drugs predispose patients to develop these infections because they target the immune system. So this is a double edged sword. This provides benefits to patients with these conditions based on their effect on the immune system.

But in addition the effects on the immune system also predispose patients to develop these infections and that's why it's so important for physicians and other healthcare providers to be very well aware of it.

We've been concerned about the possibility that there is infection since the products were initially approved and this has been in labeling from the very beginning, they've been warning about these infection including fungal infections.

What's new with our announcement today is that we became aware that some physicians may not be considering the possibility of these fungal infections early enough, so we want to raise the awareness of the possibility of these infections.

So far the companies have been fully cooperating with our efforts here.

Susan Cruzan: Thank you, can we have the next question?

Coordinator: Our next question comes from Jared Favole with Dow Jones, your line is open.

Jared Favole: Hi, thank you all for taking my question. I guess I had two, one I wanted to make sure that I thought I heard Dr. Siegel say that they were black box warnings? And then my follow up is I was wondering if there was any development yet on whether there's going to be warnings added related to the fact these drugs may cause cancer in adolescents.

I know that was something you all were concerned about back in June.

Jeffrey Siegel: Right. So your first question is whether this is going to mean changes in the black box warning?

Jared Favole: Yeah.

Jeffrey Siegel: Yes, the black box warning is intended to communicate safety concerns, particularly with where there was concern it could have an effect on who should be treated and on training those physicians to include the safe use of the product.

And we believe that this particular situation does call for changes in the box warning to make sure that healthcare providers are fully aware of the physicians and what they can do to deal with this.

In terms of the issue about changes to labels or malignancies in children, in our early communication in June we said that there were a number of other analyses that we were conducting and we're still in the process of doing that.

We gave a six month time line and we intend to use that timeline.

Jared Favole: Okay thank you for your - thank you for answering that.

Susan Cruzan: Thank you, next question please?

Coordinator: Our next question comes from Ricardo Alonzo-Zaldivar with Associated Press, your line is open.

Ricardo Alonzo-Zaldivar: Hi, thanks for taking my question. And you said the Mississippi and Ohio River Valley and I was wondering, can you give that to us in terms of the prevalence of this fungal infection by state?

Because you're talking a large part of the country and I'm thinking it might be more concentrated in some states than in others within that region.

Jeffrey Siegel: That's a good question. We don't have the exact breakdown now. The usual way of characterizing the endemic area is that whole broad region states that lie along side the Mississippi and the Ohio River Valley.

I can't tell you right now if there are particular states that were more common than others.

Ricardo Alonzo-Zaldivar: So you're basically saying the whole middle of the country.

Jeffrey Siegel: That's correct.

Ricardo Alonzo-Zaldivar: Okay, and a follow up question...

Jeffrey Siegel: I will say that 80% of the cases that we reviewed occurred in that area, that region.

Ricardo Alonzo-Zaldivar: Okay. And a follow up, can you give us a little bit more detail on what this fungal infection histoplasmosis is like? You said it affects the respiratory system but could you elaborate and talk about how it progresses?

How something like this can get so out of hand?

Jeffrey Siegel: I'm going to ask Dr. O'Shaughnessy to answer that question.

Elizabeth O'Shaughnessy: Histoplasmosis is called (dimostic fungus) (unintelligible). That means it has two forms, whether it's in the body or in the soil. So it's located

in the soil and it's very - grows very well in areas in those Midwestern states that we mentioned.

And it's found in places where there are lots of bat droppings and bird droppings. So like caves, that kind of thing. It gets progressive generally in patients whose immune system is affected for some reason.

For example, the patients we're describing today who on the TNF blockers. So it would generally starts off as a pulmonary infection and then in some cases it can actually spread through the body and affect other organs.

And these patients can become severely ill.

Ricardo Alonzo-Zaldivar: Thank you.

Elizabeth O'Shaughnessy: You're welcome.

Coordinator: Richard Knox with National Public Radio, your line is open.

Richard Knox: Yes, thank you very much. Among the 21 you identified with delayed diagnosis, how many deaths were there? Also what is the treatment and is this usually a manageable infection if the - if caught early?

Jeffrey Siegel: Those are good questions. So of the 21 cases where we had enough information to determine that diagnosis and treatment were delayed, 12 of these 21 patients died.

The treatment is an area that differs between the different fungal infections and the seriousness of infection. With the most serious forms of infection, the

ones that we're primarily talking about today, these systemic infections are treated with a drug called amphotericin B.

This is a drug that's efficacious against these systemic infections but also can be highly toxic. So the decision to start someone on amphotericin B is not a decision that's made lightly.

And the idea of treating people before a definitive diagnosis can be made is also something that's not to be taken lightly. But in patients who have a serious systemic infection, it's compatible with and the patient is at risk for histoplasmosis, those would be the patients for whom this would be considered.

And again we want to emphasize that we think that this decision should be made in consultation with an expert in the field of infectious disease.

For other fungal infections on the list, here is one, Dr. O'Shaughnessy see if you want to comment on that?

Elizabeth O'Shaughnessy: Well in my cases of histoplasmosis and the individuals may not require any treatment. But certainly in patients who are immunocompromised the moderate to severe disease, they do require fairly intravenous amphotericin B to start off with, and then at later times those patients are often switched to an oral kind of those.

So those are the two antifungals that would be mostly used in patients with moderate to severe illness.

Richard Knox: Can I ask another thing?

Susan Cruzan: Yes, go ahead.

Richard Knox: This is a little bit - this is not related to what I just said. But you mentioned this is - you're doing this under new authority, could you say precisely what new authority allows you to do what you're doing?

It sounds like you've done this in the past without the actual authority.

Susan Cruzan: When this is under the FDAAA legislation and I gather it's under the REMS where FDA can actually request or require new safety information. If Jeff can elaborate on that I can get a specific answer for you and email that to you.

Jeffrey Siegel: I think I can give you a little bit of information about how this plays out and the way these things are done. Before FDAAA when the FDA became aware of a safety concern, we would initiate discussions with pharmaceutical companies or sponsors and discuss the changes to the label.

And those changes would be made by agreement between the sponsors and the FDA. There has been concern raised in certain situations this may lead to delays in taking definitive action in communicating this to the public and revising those product labels.

The new authority that this legislation gives us, allows the FDA to make the determination if this is a serious safety concern and to determine what changes need to be made to the label.

Richard Knox: So this happened faster than it would have been in the past?

Jeffrey Siegel: It's hard to say, but we're trying to take prompt action and we believe this - working with you this information will be communicated very promptly to the public.

Richard Knox: Thank you.

Susan Cruzan: Do we have another question please?

Coordinator: Our next question comes from Andy Pollack of the New York Times, your line is open.

Andy Pollack: Yes, thanks, I have two questions if I may. One, Dr. Siegel this first case you looked at sounds awfully familiar, like the gene therapy case that arose last year.

Is that what prompted this review?

Jeffrey Siegel: So I really can't give you details on exactly what the case was. But I do have to say that learning about this case and the gene therapy file did raise questions exactly the issues that we're talking about here.

Andy Pollack: Okay. The other question I had as you - I think you mentioned that the fungal infection is already in black boxes on all these products. Is that correct and if so, what does that say about the effectiveness of black box warnings, if the warnings seem to be going unheeded?

Jeffrey Siegel: Good question, let me try to address that. So first the different labels have somewhat different information. And this has occurred for a variety of reasons.

For one thing the safety of the different products does vary from one to the other and there have been safety concerns that have risen with one product that we weren't certain would be true of the other products and they have been added, information to the other product labels at a later time.

So not all the labels are identical. So I don't believe it's accurate that serious fungal infections are in a box warning for all four of the products.

Andy Pollack: I see.

Jeffrey Siegel: We are going to make those box warnings more uniform with respect to fungal infections now. In terms of your other question about the effectiveness of box warnings, we don't want to give the impression that these conditions were neglected.

The physicians who in this case with the TNF blockers are aware that these products are immunosuppressants.

And this prognosis can be a particularly difficult condition to diagnose. It's important to think of this to determine which patients are a particular risk and it can mimic many other conditions.

In addition, even if physicians guess the appropriate diagnostic tests there are situations where those tests may be falsely negative leading the physician off the path of making the definitive diagnosis.

So we think really the new message here isn't that we weren't aware that this might happen, but to be aware that this is under diagnosed and that it's important to identify patients who may be at risk and identify early.

Susan Cruzan: Did that answer your question?

Andy Pollack: Yeah, thanks very much.

Susan Cruzan: Okay, we can take the next question please.

Coordinator: Susan Heavey with Reuter's News your line is open.

Susan Heavey: Just to follow up on that, for the products that do already have fungal infections mentioned in a black box, can you just explain sort of practically or logistically how you're going to strengthen such warnings so that there's more awareness drawn.

Jeffrey Siegel: Well clearly we're going to make sure that all the box warnings state clearly that fungal infections including in particular histoplasmosis which is the main one that's come to our attention as having been missed in a number of cases.

So that will be highlighted in the box warnings. In addition we are bringing to the attention of healthcare providers the importance of determining patients who are at risk of histoplasmosis.

So that's a second consideration. And the third one, which is new is the idea of considering empiric anti-fungal therapy in patients who have a condition that may represent histoplasmosis in patients who are at risk.

Susan Heavey: Thank you.

Susan Cruzan: Can we have our next question please?

Coordinator: Catherine Larkin with Bloomberg News, your line is open.

Catherine Larkin: Thanks for taking my question. I was wondering if Dr. Siegel or anyone else at the FDA can quantify the total number of deaths that have been reported including from infections other than histoplasmosis? There's some vague language in the release and I wanted to see if we could get a total number.

Jeffrey Siegel: So first let me go over the numbers that are in the press release so we're on the same page here and then I'll try to answer your question as best I can more generally.

So in our review, we identified 240 reports of histoplasmosis. Twenty one of those reports indicated that histoplasmosis was not recognized initially and of those 21, 12 patients died.

The total number of deaths was 45 among all the cases, all the 240 cases of histoplasmosis. Does that answer your question, or...?

Catherine Larkin: The release also says in addition to the 45 deaths then with the 240 cases, the release also says that the FDA is also received reports of cases including deaths from other fungal infections in patients receiving TNF blockers.

Do you know how many deaths were included there?

Jeffrey Siegel: With the other fungal infections? We don't have those numbers but in comparison to histoplasmosis case it was considerably smaller.

Catherine Larkin: Thank you.

Susan Cruzan: Okay. I mean that's really all the numbers that we can provide to you today. Can we have the next question please?

Coordinator: Elizabeth Mechcatie with Rheumatology News your line is open.

Elizabeth Mechcatie: Hi (Mechcatie). I wondered among the 240 cases were there more, were there any diagnoses for which these drugs are used fro that are more common and any age group that were more commonly affected?

Jeffrey Siegel: I'll call on Dr. (Steve Redonas) to help with that.

(Steve Redonas): Hi. Most often reported indication was in rheumatoid arthritis patients, roughly 52% of the cases were reported in RA cases.

Elizabeth Mechcatie: Okay. Of all ages?

(Steve Redonas): All ages were included in the report.

Elizabeth Mechcatie: Including pediatric cases?

(Steve Redonas): There were some pediatric cases, yes.

Elizabeth Mechcatie: Okay. And are there any other - anything else on that question? They were just - and the rest were evenly spread out, or...?

(Steve Redonas): Yes, if you want the age, the median age, the mean age was 47 years of age. And the ranges were from 8 years of age to 86 years of age, so they range throughout the whole age range.

Elizabeth Mechcatie: Okay, and that's for the 240 cases.

(Steve Redonas): Correct.

Elizabeth Mechcatie: And are there any other fungal infections worth mentioning that have been associated with the drugs?

Jeffrey Siegel: One particular one that's come to our attention is coccidioidomycosis which is prevalent in the Southwest of the United States, but also blastomycosis.

Elizabeth Mechcatie: Excuse me?

Jeffrey Siegel: But also blastomycosis?

Elizabeth Mechcatie: B L A S T O?

Jeffrey Siegel: That's right.

Susan Cruzan: They are listed in the press release.

Elizabeth Mechcatie: Okay, okay, I didn't see that. All right, thank you.

Susan Cruzan: Right, and I think that we had mentioned what the histoplasmosis...

Elizabeth Mechcatie: Right, right.

Susan Cruzan: The blasto...

Elizabeth Mechcatie: Right. Okay thank you.

Susan Cruzan: All right. (Kelly) do we have any further questions?

Coordinator: yes, we have a question from Miranda Hitti from Web MD, your line is open.

Miranda Hitti: Thanks, but actually my questions have been answered.

Susan Cruzan: Great, thank you. Do we have any final questions (Kelly)?

Coordinator: Yes, we have one from Donna Young with BioWorld Today. Your line is open.

Donna Young: Hi, thank you. I just had a question again going back to the FDAAA. Is this the second or third time that they've actually used their authority under FDAAA because I know when they did it with Amgen that that was what - that was actually the first time that they came to a disagreement.

They had previously sent out letters to people under FDAAA's name, they would have to change their labeling, but with Amgen they could not come to an agreement so FDA had to then actually use their authority.

Do you know if this is the second time?

Susan Cruzan: I'm sorry, Donna is this related to the issue today?

Donna Young: Yes. Under the FDAAA amendment that, the question that was asked earlier as stated in the press release that FDA had to use their authority under FDAAA for this.

So is the second time since FDAAA became effective that that...

Susan Cruzan: No, I think we have had a couple of cases but Donna we can look into that and get back to you if that's okay.

Donna Young: Great. And then also can you clarify again going back again to the deaths, were there actually any pediatric deaths when you talked about the cases, the 240 cases. You said that there were some pediatric cases but were there any pediatric deaths?

Jeffrey Siegel: We are not aware of any pediatric deaths.

Donna Young: Okay, thank you.

Susan Cruzan: Okay. And do we have one last question? We will need to wrap this up today.

Coordinator: Yes, our final question comes from Carl Sears with NBC News.

Carl Sears: Yes, are there competing drugs on the market that are just as effective but carry less risk in treating these target illnesses? Do doctors and patients have an option to take other drugs without these consequences, possible consequences?

Jeffrey Siegel: That's a question that physicians always ask themselves. And unfortunately we don't have the information that would let us answer that question.

The type of clinical trial that would be necessary to answer that question would be what we call a head to head clinical trial where people would be randomized with the TNF blocker versus another product.

And those types of products are rarely done. There are a variety of efficacious products in rheumatoid arthritis and for the other conditions, but these products are approved for generally speaking.

But we can't say that they're equally efficacious. And we also can't say for sure what the relative risk of these particular infections is with the TNF blocker as compared to other products. Good question but we really don't have the information to answer that.

Carl Sears: Thank you.

Susan Cruzan: I think that was our last question so we will wrap up the call today. Again if you have additional questions you can email Susan Cruzan, susan.cruzan@fda.hhs.gov and Rita Chappelle, rita.chappelle@fda.hhs.gov.

Thank you all so much for joining us today. Again the information is posted on FDA's website with the press release and the CDER website with the healthcare professional piece. Have a great day.

Coordinator: Thank you for participating in today's conference, you may disconnect at this time.

END