

Families of Spinal Muscular Atrophy

Transcript of SMA Clinical Trials Chat Questions Chat, Thursday, February 15, 2007

The following transcript has been 'cleaned up' – questions have been matched with answers, identifying information has been removed, and the doctors have had a chance to review the information for clarity and accuracy. Some questions were not answered during the chat and have been answered here. However, typos and other errors may still exist. Questions that were submitted ahead of time are at the end.

administrator: Hi everyone and welcome to the FSMA chat room. Today's chat subject is Clinical Trials, and our guest experts are Dr. Sandra Reyna and Dr. John Kissel. Dr. Reyna is the project manager for Project Cure SMA in Salt Lake City and Dr. Kissel is a researcher and specialist in SMA at the Ohio State University and a Project Cure SMA Team Investigator.

hv: Once neuronal apoptosis takes place in an SMA I patient (as evidenced by paralysis and respiratory weakness) to what extent will any kind of SMN protein upregulation be effective?

dr_kissel: Excellent question, and in a sense, that is the \$64,000 question. You may well be correct that upregulating SMN may NOT have much of an effect if the motor nerves are already dead. The honest answer, though, is that we just do not know. What many investigators are hoping for is that some of the motor nerves may not be totally dead, but rather just very sick and salvageable, so that upregulation of SMN2 may still be effective. Other mechanisms may also be operative.

sp : Hi Dr Kissel, is any SMA trial test specifically crafted by type (1, 2,3) or is it generic?

sl : What are the inclusion and exclusion criteria for the valproic acid study?

dr_kissel : Most trials of SMA are targeted specifically to one group, and up to this point, most studies have focussed on the type 2 and 3 patients. We don't have space to go into inclusion/exclusion criteria for all studies, but they are available on the Project Cure SMA web site www.projectcuresma.org. Since the genetic defect is the same for all three types, we are hoping that what helps one type will help the others. Project Cure is also planning on future trials in adults, as well as patients with other types as well.

dr_reyna : Project Cure SMA submitted an adult SMA study proposal to the FDA for review and it has been approved and we are in the last stages of IRB and other regulatory final approvals. We expect to be able to announce this new clinical trial in few weeks. It will be a single site study and Dr. Jihn Kissel is the principal investigator at Ohio State.

gr : Have any trials been done on erchonia laser therapy as a way of slowing down SMA symptoms to provide the best optimal health of the nerves & cells to counteract this disease?

dr. kissel: I do not know of any studies in SMA using this therapy.

ll: If one has taken valproic acid in the past can they be allowed in the study?

dr_reyna : First you must meet all inclusion criteria in order to be considered a possible study subject. Then, as long as you are not taking Valproic Acid at time of study enrolment, yes you may be able to participate in a clinical trial using Vaploic Acid as the study drug. If you are taking the medication currently, you will need to go through a wash out period when you are not taking any medication.

ll: Do you know how long the wash out process will be for adult patients who want to be included in the study and have taken VPA?

dr_reyna : **The typical washout period in clinical trials is 3 months.**

bt: I have read about the clinical trial network created by Project Cure SMA. Is it possible to join to this network from outside of the US, and create a clinical test location in for example Hungary? Where information can be found about it?

dr_reyna : **Our goal is to be able to expand internationally and we are currently working towards that goal by constant communication with interested international investigators.**

yz: Are there any clinical trials planned or underway for adults in North America? What about Canadian trial sites?

dr_reyna : **We have a study site in Montreal and looking for other interested investigators to join Project Cure SMA.**

sp : Did you hear lately any promising prospect in the stem cell research - after the mice success - around John Hopkins U ?

gr : Can stem cell research benefit SMA patients?

dr_reyna : **Stem cell research is still in the investigational phase where there are a lot more questions than answers so its hard to have a clear and precise answer for you.**

dr_kissel : **Stem cell research is exciting and may well eventually be beneficial in SMA patients.**

dr_kissel: **We did not address this important question during the chat. Rather than “reinvent the wheel,” I thought I would simply provide here an excellent update on stem cells in regards to SMA provided by Dr. Jill Jarecki, the Research Director of FSMA.**

There are several potential risks of stem cell therapy. One of the most concerning is that transplanted cells could develop into a teratoma, a form of cancer. This is particularly an issue when transplanting undifferentiated human embryonic stem cells directly. In order to avoid this situation, scientists are focusing on developing procedures in which pure populations of cells differentiated into a particular cell type are transplanted into patients, for example motor neurons in SMA. Deriving pure motor neurons from human embryonic stem cells for replacement therapy is currently the focus of the stem cell work in SMA being done by Dr. Hans Keirstead (<http://www.curesma.com/keirstead06.shtml>). In this case these stem cell derived motor neurons would be transplanted directly into the spinal cord itself. It is likely that undifferentiated stem cells, rather than human motor neurons derived from stem cells are being used in the Ukraine and China, and it is very unlikely that stem cells themselves will differentiate into motor neurons in significant numbers after transplantation in the body. Turning the stem cells into motor neurons really needs to be done prior to transplantation. To the best of my knowledge, Dr Keirstead is the only scientist to derive pure motor neurons from human stem cells. In addition, it is our understanding that in other countries stem cells are not being transplanted in to the spinal cord directly, but being injected in the blood stream. If the replacement cells are not placed directly into the spinal cord when treating SMA specifically, it is generally believed there would be no possibility for these cells to cross the blood brain barrier and reach the spinal cord in the numbers required for therapeutic benefit (this is why direct injection in the veins almost certainly does not have the potential to provide clinical benefit for SMA).

bt: For stem cell research: I have seen a number of promising results, I personally know a boy, who was treated at Ukraine and has progress. The problem is, that in Europe, or in the US, it is not allowed to do stem cell research or clinical test on humans, and the locations where these therapies are available - in Kiev (Ukraine), or in China - does not publish anything about their results. However a special clinical test could be organized, when the therapy is being done in China or Ukraine, and the results are getting measured, recorded and published in the US. Do you think such a clinical test would be possible to prove anything about this therapy?

dr_kissel : Good question. I know in regards to China that the group claiming success in, for example, ALS has steadfastly refused to let anyone examine their patients or critically review their work.

gr : Can SMA ever be misdiagnosed and be something else because SMA can encompass many different symptoms in each individual?

dr_kissel : Yes, SMA CAN be misdiagnosed, and I have seen many patients given the wrong diagnosis. In fact, I have misdiagnosed a few myself! Fortunately, with genetic testing, the frequency of misdiagnosis has been greatly reduced. Another important point is to be seen by a physician experienced in SMA. Even many neurologists have not seen many cases.

sp : What do you by genetic testing? Do you mean if one or both parent does not have it?

dr_kissel : I mean that the most common form of SMA, accounting for probably 95% of all SMA, can be tested for with a simple genetic blood test in the patient. The parents do not have to be tested.

ll: Hi doctors: I am 30 with SMA 3. I am ambulatory without aid. I have registered with the International Patient Registry in India. What are any other ways I can watch for the upcoming trial?

dr_kissel : We hope to start soon the adult trial at Ohio State soon, and FSMA web site can keep you updated on our progress. We obviously will publish and publicize the results when we have them.

f: Do you know when the SMA Carni-val clinical trial will be wrapping up? Is there anything you can share with us so far?

dr_reyna : SMA CARNI-VAL last study visit is scheduled for Nov 2007. We are working towards preliminary data analysis with the intention of being able to present these findings at FSMA meeting in June 2007.

a : Will the CARNI-VAL results be available to all at the conference or just the researchers?

dr_reyna : One of our leading investigators, (i.e. Dr. Swoboda and group) would be talking to the parents during the FSMA annual meeting.

a: Now that's an incentive for coming to the conference!

z: What are the most promising details related to CARNI-VAL tests, and which types of SMA benefit most?

dr_kissel : I am not sure exactly what you mean, in that the CARNI-VAL trial is blinded, so we really have no results, and not even any "hunches" yet. We, like our patients and families, are

simply waiting for the study to be finished and data analyzed.

gr : Can one parent that has a diagnosis of Charcot-Marie-Tooth been the genetic carrier that produced a child with SMA?

dr_kissel : Yes. Since the gene defects involved in SMA and CMT are completely distinct, one individual could have both. I have never seen or heard of this combination, but we do have patients in our clinic with, for example, two types of muscular dystrophy in the same family, and sometimes the same individual! So the answer to your question is “yes.”

p: I'm from Argentina. How can we be involved?

dr_reyna : The doctor leading the group in Cordova, Argentina is Dr. Alberto Rosa and the screening visits will help Dr. Rosa find the best candidates for SMA CARNI-VAL in Argentina.

nm: Are there good findings that Valproic acid is helping SMA II patients?

dr_kissel : There are some suggestive, uncontrolled data hinting that VPA might be beneficial, but it is preliminary and needs to be supported in a larger trial such as the CARNI-VAL group is doing.

ll: I have read and get a little confused about the different phases of clinical trials. Is the current trial looking for efficacy?

dr_reyna : SMA CARNI-VAL is a phase II trial which means that its main focus is to define a therapeutic dose range and to establish efficacy, side effects, and clinical toxicity of the study drug. Most clinical trials are designated as phase I, II, or III, based on the type of questions that study is seeking to answer:

- In Phase I clinical trials, researchers test a new drug or treatment in a small group of normal volunteers or to a carefully defined subject population under controlled conditions to obtain preliminary data on drug safety, to determine a safe dosage range, and identify side effects.
- In Phase II clinical trials, the study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
- In Phase III studies, the study drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
- In Phase IV studies, the post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

These phases are defined by the Food and Drug Administration in the Code of Federal Regulations.

sl : Dr Kissel, the valproic acid study for SMA adults will not be starting for a month or two. Is that correct?

dr_kissel : That is correct. All of our regulatory documents are in, and we have funding from FSMA! We are waiting for final approval of the IRB (human subjects) protocol! The study is part of the Project Cure initiative!

r38 : Are adult SMA patients that have been evaluated by multiple MDA clinic physicians over twenty years but that have a negative "gene test" routinely excluded from clinical trials?

dr_kissel : Unfortunately, they will be excluded for the time being. One likes to do studies with a homogeneous population, and unfortunately, it sounds like that patient is in the 5% of SMA patients that have a different gene defect. Of course, we still hope that a treatment for "regular" SMA will be beneficial to the other 5%.

yz: Dr. Kissel, how can we get involved in your trial?

dr_kissel : You can email our research coordinator at sharon.chelnick@osumc.edu and we can get you information, but only AFTER we have final IRB approval, probably in the next few weeks. Thank you for your interest!

ll: Do you know if travel will be paid for with the trial for adults?

dr_kissel : We do not plan to pay for travel, as the budget just would not support it. There are options for travel for people from out of town, and we help people make those connections.

f: We have heard that there are some clinical trials with hydroxyurea and phenylbutrate. Are you involved in these or do you know if any of them have shown promise thus far?

dr_kissel : A study of phenylbutyrate in children with type 2 disease was just published and was negative, but it was a relatively short duration study (13 weeks). Studies in hydroxyurea are ongoing.

sl : Who will be able to participate in the drug study at OSU?

dr_kissel : The Project Cure adult study is for ambulatory type 3 and 4 patients over age 18 with DNA proven disease.

sl : How ambulatory?

dr_kissel : They need to be able to walk 30 feet without assistance such as a cane, crutches, or braces.

nm: Our 26 month daughter risen from crawling to using a walker and now walking with crutches, her neurologist and other doctors are very excited for her and we believe it's a miracle and she's also taking Valproic acid which may also be helping. We live in Miami, FL

dr_kissel: That is great that she is doing so well! That is always good news.

bt: There is a drug called PTC124 created by PTC therapeutics, which is developed to cure genetic disorders where the disease caused by a point mutation in a gene. They are testing it in phase II clinical tests for cystic fibrosis and Duchenne muscular dystrophy, and if the results are positive, they are planning to extend it to other diseases like SMA. Do you have any information about if a clinical test is getting planned for PTC124 in SMA? Does FSMA or ProjectCureSMA plans to support a clinical test of PTC124 for SMA?

dr_reyna: I don't have an answer for you at this time. I can look into it and get back to you later.

dr_kissel: I would again like to thank Jill Jarecki for providing us with the following information on PTC124, which is a drug designed to read through stop codons.

PTC124 is a compound designed to fix a certain type of genetic defect called a nonsense mutation (where the mutation tells the gene to "stop" producing), which is found in some CF and DMD patients. This type of genetic defect results in truncated protein, and drugs like PTC124 allows full sized protein to be made, rather than the short protein found in some CF and DMD

patients. This is not the type of genetic defect that occurs in SMA, either in the mutations in the SMN1 gene that cause SMA or in the second SMN2 gene in humans that doesn't make much SMN protein. In SMA, the SMN gene is usually gone. For the remaining SMN2 gene, an internal chunk of the protein is missing due to a different type of mutation that causes mRNA splicing to go wrong. Therefore, it is unclear biologically how compounds like PTC, called read-through compounds would help in SMA. However, there has been some data collected at the Lorson Lab at the University of Missouri indicating that read-through compounds can result in more SMN protein in patient fibroblasts in cell culture. The cell culture result is somewhat unanticipated due to the different nature of the genetic defects in SMA, compared to CF and DMD. Because the biological mechanisms is hard to understand, we are reserving judgement on this class of compound until we see some SMA studies in animal models of SMA (mice and fish) need to be completed to assess whether this is also the case in animals. These studies are now underway. Once studies those have been completed we will have a better idea of whether this drug is a possible candidate for SMA. At this point in time, that remains unclear. Hopefully, we will have a better idea of this soon.

ll: Will the adult study be placebo controlled?

dr_kissel : For the first six months, it will be placebo controlled, and then everyone will get the drug.

hv : Are there any clinical trials planned involving oligonucleotides?

dr_kissel : To my knowledge, there are no clinical trials currently planned with oligonucleotides, but there is much basic research going on in this area. It is really a "hot" area of research now for all of the genetic diseases.

sp : Do you know if there is a clear and concise definition on who is type 2 and who is type 3. Ours is diagnosed 3. For 3 in general it says that they can sit by themselves and they can walk by themselves once put on feet... I am very confused because I have noticed the floppiness of my baby when she was 3 month old but the pediatrician never agreed until she was 18 months old to send her to a specialist. She was breast fed, hence maybe things were delayed. ... I am afraid she is type II because her walking is gradually decreasing now at 30 months... Who is clearly classified as type 3?

dr_kissel : This is a confusing area, but most clinicians and researches use the maximal motor milestone as the major defining feature for typing. Thus, if your daughter walked independently, even for a short time, she is considered a type 3.

There have been a lot of questions about the different types of SMA, and whether trials will be ongoing for each type. One other vitally important thing to remember is that since the basic genetic defect; namely the deletion of the SMN1 gene, is the same for all types of SMA, we are hoping that whatever we learn to help one type of SMA will also help the other types.

f: Besides valproic acid, do you know of any other promising drugs on the horizon?

dr_kissel : There are about 8 drugs now that show promise, all of which are already being produced. There are several other agents that have been identified, and more being screened all the time, for compounds that are promising but not yet available drugs.....I hope that makes sense.

f: Could you give me a few names of the 8 so I can keep up with the findings?

From Jill Jarecki, FSMA Research Director:

There are a number of novel drug programs underway for SMA. The goal of each of these projects is to increase SMN protein levels from the SMN2 gene. All of these projects are still in the pre-clinical phases of drug development, which occur before testing in humans begin. These include projects ongoing at deCODE Genetics, Paratek Pharmaceuticals, PTC Pharmaceuticals, Vastox, and the SMA Project (NINDS). In addition, several drugs in development for other disease may prove to have utility in SMA after further studies in SMA cellular and animal models. These could potentially include SAHA, PTC124, and Trophos19622, and PBA derivatives. Of course, several repurposed FDA approved drugs are already in clinical testing for SMA, including VPA, Hydroxyurea, and PBA.

z: Is there a way to measure how many copies of SMN 2 one has? What is the relation to copies to type?

dr_kissel : SMN2 copy number can be measured, and in general, the more SMN2 copies, the milder the disease. SMA 3 patients for example, usually have 3 or 4 copies of SMN2, whereas SMA2 patients have 2 or 3 copies. Just last week, I saw a patient who did not start having symptoms until age 23, and he has 5 copies of SMN2.

d: Does the anticipated effect of VPA (valproic acid) and others of that ilk actually serve to 'heal' or 'preserve' existing muscle?

dr_kissel: We don't know yet exactly what VPA may do or not do. As mentioned above, we would certainly hope that VPA could preserve function, but if the motor nerves are just sick, and not all the way dead, it could improve strength as well.

bt: There is a protein called myostatin. It was discovered, that if the gene forms this protein is getting blocked (or is not working), and then the body produces more muscles. Do you know about if a clinical test is planned in the area of how myostatin blocking affects an SMA patient?

dr_kissel: Man, you are good! You are correct about myostatin, and there are efforts going on in several laboratories looking at the effect of myostatin blockade on muscle in animal models of SMA. It may be a future therapeutic option.

ll: Can anyone go to their neurologist to find out how many SMN2 copies they have? Will that be measured in the trial?

dr_reyna : SMA CARNI-VAL did measure SMN2 count on every study patient. Your neurologist may order a DNA analysis.

hv : Since the SMN protein is a neuronal apoptotic inhibitor protein, why isn't more attention being given to other "naips" such as survivin and caspase inhibitors that have been shown to prevent neuronal loss in animal models of head injuries and stroke?

dr_kissel : Good question. I think the operative word is "attention". There ARE labs working on these pathways, and looking at their roles in SMA. Some of these other pathways have been looked at and found not to be of much importance in SMA. It gets back, I guess, to the old issue of how many eggs are you going to put in how many baskets. In this case, an important secondary question is how much basic lab results do you want/need to justify a clinical trial. I

hope that answered your question.

nm: I've seen some time ago 1 or 2 articles in the web that there may be a cure for SMA within 5 years. Have you seen this or do you believe?

dr_reyna : SMA research has evolved very quickly in the last 3 years. So I believe that if we keep working hard at trying to find a treatment for SMA we are going to be successful by answering many questions we've had no answers to not so long ago.

gr : How do you know if the doctor you are seeing has all the up to date information are talking about tonight?

dr_kissel : I think the best way is to ask them directly what is new in the field, and then to ask them some questions like you and the rest of the group are asking tonight. I have been stumped many times by patients who have done more "homework" than me, and actually knew about work or a drug that I did not know about. Usually, you can tell by how he/she answers some basic questions whether 1) they are up to date; and 2) more importantly, whether they care if they are up to date!

sp : Dr Reyna, do you believe that a 500 mg or so a day of creatine supplement for a 30 months old SMA 3 is OK? I know I missed the last panel but there was no reference on the transcript... Sorry for diverging a bit... Knowing there is not much possible trial going on for toddlers I am determined to keep my baby stronger until something happens.

nm: My 26m daughter is taking 1cc Valproic acid 1cc Carnitine both twice daily, liver blood test are normal, do you believe she may take a higher dosage? She's 34 lbs. Her neuro doc may benefit from your info since he's given her the drug through Swoboda & your info.

dr_reyna : I can not provide any clinical advice but I can refer you to one of our experts from Project Cure SMA and have a one on one conversation.

gr : Can any children with type 2 SMA ever learn to walk on their own? Do you personally believe in your lifetime their will we a cure for SMA?

dr_reyna : I believe SMA scientists are doing everything possible to find answers to understand and learn more about SMA with the ultimate goal to find a treatment.

gr : I am going to stay positive. Thank you

dr_kissel : I do believe that we will have a treatment that significantly affects the course of the disease. I think "cure" is a word that we actually can rarely apply to most diseases.

sp : I am in Ohio, I have a 30 month old SMA type 3 diagnosed kid...I would like to know if there is any clinical trial planned in the next 6 month...

dr_reyna : We plan on continuing to design other clinical trials for SMA children of all types and ages.

r38 : Have any studies looked at the amount of respiratory muscle involvement in SMA 3 patients as this compares to the rate of progression of symptoms? In other words, would periods of mild hypoxia be expected to hasten the progression of this disorder?

dr_kissel : Good question that we are looking at in natural history studies and the clinical trial work.

Other questions were submitted ahead of time by users who were not able to join us:

f: The SMA CARNI-VAL Clinical Trial is using the modified Hammersmith scale, a scale that excludes a large population of children and adults with SMA. Is FSMA planning on using or funding future clinical trials that utilize the modified Hammersmith scale or will FSMA fund clinical trials that utilize scales that have less exclusion criteria such as the Gross Motor Scale?

dr_reyna : I understand that Kristin Krosschell, PT (Principal Investigator for the physical therapy group) had addressed this question with you. I would prefer to have her continue to do so and if you would like we can post her response to you as part of this chat.

f: In September, there was an announcement that there were open slots in the SMA CARNI-VAL trial. How long has the SMA CARNI-VAL Clinical Trial been extended because it could not initially find enough candidates?

dr_reyna : SMA CARNI-VAL trial made an announcement in Sept 2006 indicating that there were a few slots open for participation in the study and all slots were filled by November 2006.

f: Assuming there are positive results seen in the SMA CARNI-VAL Clinical Trial, when will patients excluded from the trial have an opportunity to receive treatments?

dr_reyna : Clinical trials are traditionally classified into four phases (Please see the classification above in one of the other questions). SMA CARNI-VAL is a Phase II study. Each phase of development leads to a greater understanding of the attributes and uses/indications of the compound in question. Our goal is to continue to follow through all phases of clinical research to analyze the effects of the test treatment and do so through FDA approval.

f: Is it true the SMA CARNI-VAL clinical trial is focusing on younger children because younger children have a greater response to this particular drug? If so, what funding and research efforts focus on the search for a cure for anyone over the age of 8 years old?

dr_reyna : New clinical trial design for SMA children are always a concern to Project Cure SMA investigators. We are constantly looking for potential study drug(s) that can be used safely in all age groups, as well as other clinical trial designs to include different study SMA groups (i.e. age groups, SMA types, inclusion/exclusion criteria, the use of other functional motor scale as a test scale, etc.)

We know that there were many additional questions submitted after the chat ended. We apologize that we have been unable to answers these questions at this time. Families of SMA would like to remind participants that while we attempt to address specific questions, this chat is designed for more general information, and specific questions relating to individual patients are better answered by personal physicians.