

## Info-research...

by : Massimo Pandolfo

Short speech by Dr. Massimo Pandolfo, at the annual General Assembly of the Canadian Association of Friedreich's Ataxia on November 6, 1999.

Good evening everyone,

It is now an annual appointment; I think that it is the fourth time that I come to bring you up-to-date with the state of research. I am therefore going to give you a short résumé of where we are at with the research, particularly trials for treatments, for we are already at the point of trying out treatments.

I think that you all know that the disease is a consequence of a mutation in the gene of frataxine and that the disease is the consequence of an insufficient quantity of this protein. This causes an abnormality in the metabolism of iron.

In fact, we find an accumulation of iron in a structure which is situated in each cell, called a mitochondrion. The accumulation of iron in this structure causes a deficit in energy in the cell and it causes oxidation damage. This is caused by the production of toxic substances called free radicals which can damage several structures in the cell.

Since a year, research has clearly demonstrated that these processes took place in the human disease, that is to say, the deficit in energy and the accumulation of iron in the mitochondria and the oxidation damage. Certain medications were tried to see if they were able to correct these defects. The first medication was tried out in Salt Lake City and it is called Desferrioxamine. It reduces the level of iron in the organism. The results are not yet available, but it seems that it has positive effects on the level of cardiomyopathy, but it is really too early to conclude anything.

On the other hand, this medication is difficult to use since it has many secondary and toxic effects. For the time being, the best choice is to try it out in a very specialized centre like that of Salt Lake City and wait for the results before deciding if there is a place for Desferral in the treatment of Friedreich's Ataxia. Another medication, idebenone, was tried out by a French group. Perhaps you have already heard of it, the last Eldorado speaks of it. Idebenone resembles a natural substance called Coenzyme Q. Coenzyme Q is present in all the cells, in particular in the mitochondria, the same structures where frataxine is found and the same structures

which are damaged by free radicals. The role of idebenone and of Coenzyme Q is a role of an antioxidant. Idebenone can therefore prevent the damages caused by iron.

In a laboratory system, a French biochemist demonstrated the efficiency of idebenone in protecting against damages caused by iron. Following these encouraging results, it was decided to attempt giving this medication to patients in order to see if there was a result.

A small number of patients started to take idebenone in France and in Italy. In Italy the medication is immediately available, unlike here. The results with four French patients have just been published and are very encouraging, especially in cardiomyopathy. The disease causes hypertrophy of the heart which is diminished in a perceptible manner in the patients taking idebenone. The dimensions of the heart were within the limits of the normal after a few months of treatment.

Myself, I have followed three patients in Italy who were taking this medication. I did the follow-up by e-mail and I also saw two patients on the occasion of a trip to Italy this summer. At the moment it is difficult to judge the effect of idebenone on the neurological disease on coordination.

Following this preliminary experience, we decided to start a pilot clinical study which would take place in Montreal. A part of the study would be held at CHUM and we are thinking of recruiting around ten patients. I have just received the authorization of the ethical committee of CHUM, so the project is authorized. We have funds which come from the most part from your association and we have also received a donation from a family in Boston.

We were therefore able to buy the medication, since because we do not have the collaboration of the manufacturer, we have to buy it. We have enough of the medication to start study, which is planned for one year. We are thinking of recruiting ten patients from CHUM and another ten from Centre Marie-Enfant. These patients will be adolescents and will be followed by Dr. Michel Vanasse of Ste-Justine Hospital, whom most of you know. This will be an open study, that is to say, we will give the medication to all of the patients and each patient will be his own monitor.

The patients will be evaluated from the clinical, cardiac and neurological points of view at the beginning of the study, then after 3, 6, 9 and 12 months. The goal of this study is primarily to see if there is toxicity, if the medication is safe.

We do not think that it should have any secondary effects since it is a natural product, but we must test it just the same before distributing it. And we are also going to try to confirm that the medication causes an improvement in a neurological respect and in a cardiac respect. At the same time as this pilot study, there will be a multi-centric study, that is to say, it encompasses many clinical centres in North America and in England.

This study will begin in autumn 2000 when the pilot study will be over. The data from the pilot study will be used to set up the multi-centric study. We hope to recruit the

largest possible number of ill persons. These studies will take place in Los Angeles, Jackson (Mississippi), Philadelphia, Portland (Oregon), London in England and at the Mayo Clinic in Rochester (Minnesota).

This type of studies will allow us to recruit a large enough number of patients in order to have a very good evaluation of the effect of idebenone. Having the structure established will eventually allow us to evaluate other medications. Idebenone is not the last word; other medications will perhaps function better. Another point which is important for you to know is that we hope to very soon have a mouse model of the disease.

As you perhaps know, there is no animal equivalent of the disease. Some French researchers tried to create an animal model by using a technique called <<Knock-out>>. They destroyed the frataxine gene in the mouse but the complete destruction of the gene brings about the death of mice right from the first stage of embryonic development. It is therefore not a good model. In collaboration with a researcher from Salt Lake City, we developed another model which is a copy of the human disease, with the same genetic mutation which we find in the patients. We have 16 mice which carry this mutation in a heterozygous state, that is to say, that we have sixteen mice carriers. We are going to do crossbreeding between these mice to have homozygotes, which should be like the human disease. We do not know if these mice will be viable, if they will be afflicted with the disease. The gestation time of a mouse is three weeks and they reproduce themselves starting at sixteen weeks, it goes much faster than in a human.

Therefore starting in December or January, we should have homozygous mice. I do not know if these mice will be a good model of the disease but I have much hope. An animal model would help us enormously for the study of the pathogenesis of this disease, the biochemical processes, and also to try out treatments. It is much easier to try out treatments in a mouse than in a man. I hope that at your next assembly, I will be able to announce to you the results of the pilot study and speak to you about the studies in mice. I will perhaps also be able to speak to you about new medications. That is all that I wanted to tell you this evening, I will answer your questions. Thank you for your attention.

I thought that I would have several questions after having announced the existence of medications which seem to have an effect on the degenerative process of the disease. This is not a symptomatic medication. The medication seems very efficient on the level of the heart. There is even an improvement of the cardiomyopathy. On a neurological level, there does not seem to be an improvement but at least a stabilisation. A slowing down or a stop of the disease would already be something. When will the clinical trials take place? We must have the authorization of the ethical committee and of research, and it is done. I have just ordered the medication. I should have it in 5 to 6 weeks. I am going to recruit patients at the end of November and beginning of December and I would like to begin giving the medication in December or January.

How will the choice of patients be made? We have enough medication to treat ten adult patients from CHUM and ten adolescents from Marie-Enfant. I have an ataxia clinic at CHUM with Dr. Marchand. I will begin to recruit the patients who will come to

the clinic starting in the month of November. We cannot have medication for more than ten patients, so we will choose the patients who are already being followed by the clinic. Can I be chosen? Why not? There are certain restrictions which we are going to see with each of the ill. If you are being followed by the clinic or you make an appointment, you can be taken into consideration. You must sign a consent form and be well informed of the study (risks, etc.). If you answer to all of the criteria and you sign the consent form, you could be chosen. Evidently there is a problem of the number chosen; we cannot take more than ten patients. Idebenone was first developed for Alzheimer's disease. But the results are not convincing. Therefore the company has no interest in commercializing this medication. We did not have the support of the company.

I sent a request to have the medication for a clinical trial, the answer was no. We are carrying on negotiations in order to change their minds. Which patients are you going to recruit at CHUM? Adult patients who use a wheelchair, of whom the diagnosis has been proved by a molecular test and they must not have other diseases, not be pregnant, not be breast feeding.

The adolescents must walk. Do we expect to have better results in this group of younger patients and those who walk a little? Yes, if there are not any other diseases. As each patient will be his own monitor, it is well.

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