Cornea a potential way to diagnose Small Fibe

Drug authority accelerates approval process of ARA290

Jules Prast

The trials with ARA 290, an experimental drug developed to treat sarcoidosis induced small fiber neuropathy, have continued into international phase 2c. What hurdles will have to be taken before it is available for patients? An interview with Chief Executive Officer of Araim Pharmaceuticals Inc., Dr. Anthony Cerami, who is developing the new first-in-class drug.

Dr. Tony Cerami.

Biochemist Dr Antony Cerami strongly believes in the potential of ARA 290. However, it will be quite some time before it is approved for use in sarcoidosis induced Small Fiber Neuropathy (SFN). ARA 290 is a unique compound that turns off inflammation and demonstrates the potential to reduce neuropathic pain and repair damaged small nerves. This may lead to a reduction of pain and an improvement of autonomic symptoms such as dry eyes, palpitations and dizziness. Moreover, the results of clinical trials give hope that ARA 290 can diminish the chronic fatigue many patients suffer from.

Cerami talks about the drug as a *disease modifier*, a drug that does not only control symptoms, but also intervenes in the underlying syndrome of small fiber neuropathy. However, here he encounters another problem: 'Such a drug is completely unique, a new invention. Drug authorities find it difficult to believe that this is possible. As we hope to treat neuropathic pain, we must address the regulatory agencies that evaluate ARA 290 as if it is an analgesic pain killer. Traditional pain killers have immediate pain killing results, and also have all the side effects that have become such a problem. Although ARA290 can turn inflammation off immediately, the repair of damaged tissue takes time.'

A delicate equilibrium

By mentioning drug authorities Cerami alludes to regulatory agencies such as the FDA in the USA and the European EMA in London. In pharmaceutical research these authorities were established to protect patients from dangerous or ineffective drugs. Can drugs in the process of development be safely used? Has it been proved according to existing scientific standards that a drug acts as it is claimed to act?
The FDA and the EMA are important parties because they decide if drugs are admitted to the American and European markets. It is a glimmer of hope that the American FDA recently decided to give ARA 290 a special status (fast track), meant to supply additional regulatory support, which could make the drug available sooner to the patient. At the EMA an application is on its way for ARA 290 to be incorporated in the granting program Horizon 20/20,

ARAIM

Araim Pharmaceuticals Inc. is a small American biotechnical company with its main office in the state of New York (www.araimpharma.com). Dr Anthony Cerami is the CEO of the company. Araim concentrates on developing new treatments for unexplained diseases such as small fiber neuropathy with sarcoidosis. The research on ARA 290 started about thirteen years ago.

ɔer Neuropathy in sarcoidosis

encouraging twenty new orphan drugs to be approved by 2020. This could help fund the incredibly expensive process to develop a drug. Cerami has been impressed by the regulatory agencies in the Netherlands and in Sweden, which they have met with to receive guidance. 'These agencies were intrigued by the unique mechanism of action of ARA290 and the absence of side effects.'

The evaluation criteria of the drug authorities imply finding a 'delicate equilibrium' (in the words of Cerami) in the research into the activity of ARA 290. At present trials are performed in subjects in the Leiden University Medical Center (LUMC) in the Netherlands and the Cleveland Clinic in the American state of Ohio, a national treatment center for patients with sarcoidosis, to establish the right dosage of ARA 290. 'Our first goal is getting approval for the drug for patients who have the disabling complication of chronic sarcoidosis.' During and after the trials subjects and a control group get extensive questionnaires to assess their sensation of pain and state of their autonomic dysfunction. 'Trials must be run impeccably to protect the patients and impress the regulatory agencies', Cerami says.

Dizziness and fatigue

Cerami is convinced that ARA 290 has the potential to repair small fibers which are damaged in an inflammatory disease such as sarcoidosis. Research in experimental animals has shown that inflammation in one part of the body can affect nerve fibers in other parts of the body and that ARA 290 can partially repair this damage. The unanswered question is: is this also true for humans?

Cerami says, 'It is a problem that small fiber neuropathy is under diagnosed. Patients experience its symptoms, not only the pain but also the effects on the autonomic nervous system. The transmission of information is disturbed due to the loss and damage of small nerve fibers. This can cause a confusing range of symptoms of dizziness and fatigue, dry eyes, as well as heart palpitations and problems with sweat secretion. These symptoms are not only seen in sarcoidosis but also in other chronic diseases or as an isolated syndrome. Many patients feel misunderstood by their doctors. This is caused by doctors being unfamiliar with the underlying illness and considering the complaints to be indistinct. To add to the confusion each patient usually presents slightly differently.'

Minor importance

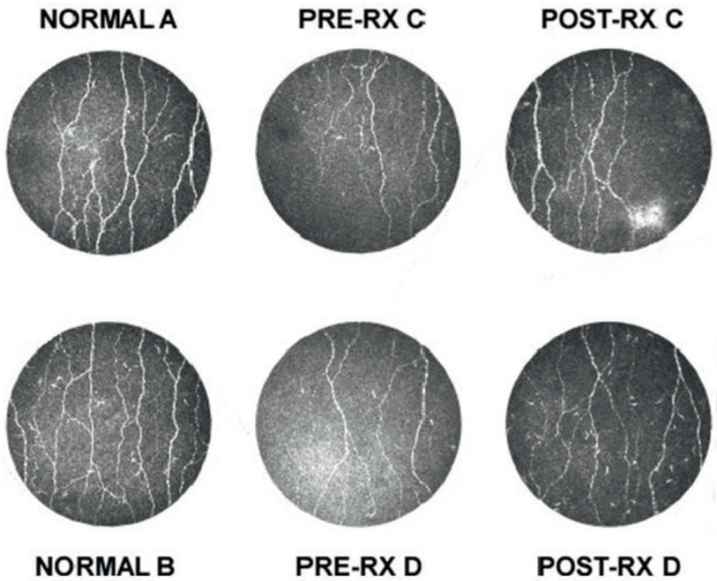
According to Cerami patients with sarcoidosis are at an advantage because in this respect they stand up for themselves as a group, even more so since in 2005 the Dutch neurologist Elske Hoitsma demonstrated in her thesis called *Small fiber neuropathy: a novel finding in sarcoidosis* that sixty to seventy percent of this population suffers from symptoms of small fiber neuropathy. 'But doctors still don't recognize this,' Cerami believes. 'Perhaps slightly more in Europe, but hardly at all in the USA.' In Europe he regularly comes across practitioners treating sarcoidosis who consider small fiber neuropathy to be a problem of minor importance.

So there you are with something new, with a medical innovation in potential for an unexplained disease, the diagnosis of which is difficult to establish. How can you achieve acceptance for your hope that with a new drug it is really possible to treat this illness? Where do you locate medical specialists who are interested in being ambassadors for ARA 290? How do you engage with expertise in sarcoidosis, which is programmed to think that granulomas are the only challenge, and consider other symptoms to be 'vague'?

Breakthrough

The trial research has rendered a number of significant positive insights and results that are hopeful for Cerami. As a start Araim used a technique that has been developed for patients with diabetic neuropathy, to objectively measure small fibers in the cornea of the subjects. Cerami speaks of a 'breakthrough' in the development of a clinical diagnostic protocol for small fiber neuropathy. *Corneal Confocal Microscopy*, the official term for the diagnostic tool, has been used by

Dr. Rayez in the United Kingdom extensively in diabetics to quantify SFN. Araim is the first company to apply this diagnostic method to patients with sarcoidosis: 'It is an easy non invasive examination of two minutes and the analysis is performed by computer. Any specialized treatment center of sarcoidosis should be able to perform such an examination. Patients should ask their doctors for it. The CCM machines are often found in the eye departments in hospitals.'
Patients with SFN exhibit an obvious lack of small nerve density in their cornea, which is quantifiable. 'In a phase 2 trial completed at LUMC, with Prof. Albert Dahan as the lead investigator, sarcoidosis patients with SFN gained an average of 17% nerve fiber density in their eyes following 30 days of dosing of ARA 290. This response correlates with an improved score of this group in the six-minute walk test, another important test of physical function and fatigue. These patients also indicate that their pain and their autonomous symptom dysfunction decreased and their condition improved. Cerami says, 'The results show that ARA 290 improves the chronic fatigue in patients with small fiber neuropathy, often the main problem they struggle with.'



A and B are nerve fibers in the cornea of healthy people, C and D are nerve fibers in the cornea of patients with sarcoidosis and small fiber neuropathy. The two pictures on the right are after the test treatment with ARA 29 (post-RX), the middle pictures are before treatment (pre-RX). Source: Leiden University Medical Center

A hope for symptom directed usage

Research also indicates that the effect on small fibers and condition may increase as ARA 290 is used longer. Cerami is raising funds for a phase 3 trial in which subjects are dosed for 6 months. He is in discussion about this with doctors in the Netherlands, Belgium, Germany, Sweden and the USA. 'We have to find out what is the optimal period for using the drug and what is the optimal dosage for the patient. There are indications that it is sufficient to use the drug "symptom directed" for one period depending on the symptoms and not chronically. Both this and the fact that ARA 290 is a chemical drug make it much cheaper than the present generation of biologicals.'
The first goal is to gain admission to the market for ARA 290 as a treatment for small fiber neuropathy. 'We have targeted approval by 2017,' Cerami says. He does not envisage only one medical specialist prescribing ARA 290: 'Any doctor treating patients with sarcoidosis induced small fiber neuropathy should be able to prescribe ARA290. It does not have to be a neurologist. It is possible that for sarcoidosis the drug will be prescribed by the lung specialist, because this doctor is mostly involved in treating sarcoidosis.'

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