PL37: a new hope in the treatment of painful diabetic neuropathy?

Solomon Tesfaye speaks to Nick Ward, Commissioning Editor:

Solomon Tesfaye, MB ChB, MD, FRCP, speaks about PL37; the first orally administered dual inhibitor of enkephalinases and its potential role in the treatment of painful diabetic neuropathy. Solomon Tesfaye is a Consultant Physician/Endocrinologist at Sheffield Teaching Hospitals and Honorary Professor of Diabetic Medicine at the University of Sheffield. His research projects include the epidemiology, risk factors, pathogenesis, CNS involvement and treatment of diabetic neuropathy and neuropathic pain. He was awarded the Prestigious Camillo Golgi Prize

of the European Association for the Study of Diabetes (EASD) in 2014 for major scientific contributions in diabetic neuropathy. He has had international leadership roles including chairmanship of the International Expert Group on Diabetic Neuropathy, and of NEURODIAB (2006–2009). He is also a member of the Science and Research Committee of Diabetes UK; a review panel member for the MRC, a Board Member of the Global Quantitative Sensation Testing Society; a member of the Advisory Council of the Neuropathy Trust; and Secretary of International Insulin Foundation. He has served as a member of the MRC, JDRF, NIDDK and UK NIHR scientific review panels and as a member of a Diabetes and Neuropathic Pain Review Group for NICE.

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Q Please tell the readers what first drew you to the field of diabetes & diabetic neuropathy.

As a young scientist I was fortunate to work under the renowned Sheffield researcher, Professor John Ward, who was one of the foremost clinical scientists of the 1970s and he really inspired me. Professor Ward, along with PK Thomas and Peter Watkins in London were three researchers who really advanced the field. Professor Ward began diabetic neuropathy research in Sheffield and I was able to see first-hand the impact of this condition. For example, I once saw a young lady who had a terrible foot ulcer due to her walking with a nail stuck in her shoe without realizing. The lady was simultaneously experiencing severe painful symptoms, providing a classic example of the painless and painful symptoms that can occur with this condition. This case made me question how this could be possible, and subsequently fueled my ambition to research diabetic neuropathy.

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Q In 2014, you won the prestigious Camillo Golgi Prize, the highest award on diabetic complications bestowed by the European Association for the Study of Diabetes. This must have been a great honor.

Ever since I was a young researcher it was always my ambition to win this prize, it really is the pinnacle for someone working in the 'Complications' field of diabetes and I was delighted to win the award. We have made many discoveries examining the peripheral nerve and looking at the vascular supply of the peripheral nerve, and I am thankful to the many patients who willingly volunteered for our research, undergoing local anesthetic so that their nerves could be studied. More recently our research has involved the brain imaging of patients with painful neuropathy using state-of-the-art MRI techniques. This highlighted the involvement of the spinal cord and indeed the brain in diabetic neuropathy, hitherto considered a disease of the peripheral nerves only. Many research areas have shaped my career and this award recognizes all of these. I am very passionate about research and I hope my findings can be translated into meaningful treatments and developments for patients.

Q You have several roles with national organizations & funding bodies, please tell us what your roles entail.

I am currently part of Diabetes UK's Science and Research Advisory Group, having previously been vice-chair of this group. The Research Advisory Group is responsible for the development of research strategy and prioritization of important research areas. We have to decide which research has the greatest potential to benefit the patient; we have a relatively small research budget compared with the NIHR, for example, so we have to ensure that the selected research has good translational potential.

I also work for the Medical Research Council, the largest funder of medical research in the UK. I am a panel member of the Developmental Pathway Funding Scheme (DPFS), and this involves meeting with other experts and evaluating grant proposals to decide which ones are to be awarded funding. The DPFS is designed for the development of new molecules, new innovative compounds or devices for the benefit of human health.

When evaluating proposals, we are looking for certain themes; what is the methodology and can it be delivered? Is there a clear unmet need? Is it

a UK's priority? Proposals have to be robust and demonstrate this; is the rationale good for the proposed research? Do they have the organizational setup to deliver their objectives? It is a fair system, with a wide representation of expertise from the very best institutions.

I personally think the British government does a good job in terms of the amount of funding provided for medical research. We need this funding to maintain the UK's standing in the world of research.

Q What are the key features of diabetic neuropathy?

Diabetic neuropathy is very common, with approximately 2 million sufferers in the UK. Diabetic neuropathy has several consequences; one is the numbness and loss of feeling in the feet, which can lead to ulceration, infection and amputation. Another consequence is neuropathic pain, which is experienced by approximately 20–30% of diabetic people; this originates in the feet and toes and can affect the upper limbs. There is a nocturnal exacerbation of this condition with tingling feet at night, coldness, burning, unremitting pain, which is very disabling.

Once this pain becomes chronic usually after 6 months, patients become anxious and depressed, causing them to lose sleep. Lack of sleep causes a decrease in the patients' tolerance for pain and coupled with the fact that anxiety and depression are known amplifiers of pain, you can easily see how patients get trapped in this vicious cycle. These factors impact negatively on a patient's quality of life, making them unable to function normally and impacting all areas of their life.

Diagnosis of diabetic neuropathy in the clinic is done with simple instruments, for example, the tuning fork and 10 g monofilament; however, these are crude methods and there are now technologies which can replace these. A handheld diabetic peripheral neuropathy (DPN) screening device, known as DPN-Check (Neurometrix) is already being used in the USA and can provide a patient's nerve conduction velocity in approximately 3 min. Another piece of technology that we utilize in Sheffield is the SUDOSCAN. This machine measures the electrochemical skin conductance of hands and feet through reverse iontophoresis and can diagnose neuropathy accurately in around 3 min. I think that in the UK, we need to make more of an effort to move into the 21st century with the use of cutting edge technology for the early diagnosis of neuropathy that

can benefit the patient. We are currently doing a feasibility study of using both devices in patients attending for their annual diabetes eye screening and the results are very encouraging with high patient acceptance for a combined (one-stop) screening service.

Q Why are current drugs ineffective for the relief of diabetic neuropathy?

At the present time, we do not understand the pathogenesis of pain in diabetic neuropathy or in neuropathies generally. If you are experiencing nociceptive pain – this is easily managed; however, neuropathic pain originating from nerve damage or dysfunction is a problem as it becomes less responsive to conventional treatments. For neuropathic pain, current drugs are being administered generically to all conditions, including post herpetic neuralgia, painful diabetic neuropathy and fibromyalgia. These drugs work to some extent, but we need to have a better appreciation of what is generic and applies across all of these pain conditions, and what is specific to diabetic neuropathy, for example. We also need to study the relationship of pain phenotypes to potential mechanism based treatments. Until we have this ability, our treatments will not be as effective as they could be. There is a great shortfall in the effectiveness of treatments from where we would like them to be; all the observed benefits of current treatments are, to some extent, negated by side effects. We need to look for new, novel pathways to facilitate the production of more efficacious drugs.

Q Please tell us about PL37, a novel dual enkephalinase inhibitor, which is currently being investigated.

PL37 is the first orally administered dual inhibitor of enkephalinases (DENKI). PL37 is specifically active at the level of peripheral nociceptors, increasing the concentrations of enkephalins at the very spot where the painful stimulus produces them in abundance, but where, in the absence of DENKIs, the enkephalins are very rapidly degraded by the peptidases neutral endopeptidase and aminopeptidase N. By inhibiting the enzymatic degradation of enkephalins, DENKIs elicit lasting analgesic effects, as potent as those of morphine, but without the side effects.

A sizeable synergy (sixfold compared with a twofold additive effect) has been demonstrated in rodents when PL37 is added to gabapentin or pregabalin. Therefore, it appears that patients suffering from neuropathic pain and who are

only partially relieved by pregabalin or gabapentin may significantly benefit from the addition of oral PL37 to their background medication, and it is the purpose of this Phase IIa study to validate this hypothesis, in a randomized and double-blind placebo-controlled fashion.

This potentially very important trial, taking place in the UK, will be the first of its kind to investigate the potential of an innovative drug, which can prolong the body's own natural pain-killers. DENKIs like PL37 are an exciting, long-awaited, novel class of analgesics for chronic pain conditions, such as painful diabetic neuropathy.

This molecule has been designed to facilitate control of pain, including neuropathic pain. A very good article from Michel Wurm's unit [1], provides great detail about the mechanisms involved and there appears to be a very good rationale for its efficacy.

The molecule is effectively enhancing the opioidergic system to relieve pain. In addition to this, this molecule targets a natural pathway, meaning that you do not have the side effects seen when an exogenous compound, such as morphine, is administered. Therefore, this is a potentially very effective pathway; however, the proof will be found in the clinical setting.

Q Patients are currently being recruited for a Phase II clinical trial which will evaluate the safety, tolerability & efficacy of PL37. What will this trial entail?

We are currently running in a Phase IIa early-clinical trial for 1 month, with the aim of determining if the treatment works. Some patients will receive PL37 + gabapentin or pregabalin or, placebo + gabapentin or pregabalin, to determine whether PL37 is significantly more effective than placebo.

If the results are encouraging, the next step would be a multicenter, Phase III trial with the aim of obtaining regulatory approval. Bigger and better powered studies are required over a longer duration and if the treatment is proven to work, it becomes available for patients. The Phase II trial has to analyze the drug's efficacy, measured by the improvement in pain using the 24-h Numeric Rating Scale as the primary objective but also has to evaluate the drug's safety profile. Efficacy measurements take into account the patients global impression of change and the physician's global impression of change, of which I am more interested in the patient's impression of change. This Phase IIa trial will give us extremely valuable data to inform further studies. If these further studies

have positive outcomes, it is hoped that the drug will ultimately come to the market.

Q Why have previous treatments & clinical trials for diabetic neuropathy been unsuccessful?

There are a number of possible reasons for this, first, it is evident that many of the compounds have had limited efficacy. A different aspect of this could be that our treatment targets are incorrect; we are trying to block a pathway rather than enhancing the patient's defense system. A further aspect could be that we are grouping all patients together for clinical trials.

Interesting research by Demant *et al.* [2] focused on oxcarbazepine, a previously 'failed drug', which had been trialed and had failed to obtain the required efficacy for regulatory approval. This group thought oxcarbazepine could be effective in certain populations and they split their study group into 'irritable nociceptor' and 'nonirritable nociceptor' groups and performed the same trial in each group. It was discovered that the drug had no effect on the 'nonirritable nociceptor' group, with similar efficacy to placebo. However, in the 'irritable nociceptor' group, the drug was shown to work very well.

These results suggest that maybe we should be phenotyping patients into groups, rather than lumping all neuropathic pain into one group. I believe we need to pursue a mechanistic approach, targeting better outcomes with reduced side effects and this is where the current study has opened up a new avenue of research.

Q How do you see the field developing in the next 5–10 years?

One area that in which I think there will be great developments is in brain imaging. We currently do a lot of brain imaging in Sheffield, particularly using resting state functional MRI. We recently presented one of our studies at the American Diabetes Association meeting, which demonstrated that most people with chronic pain have altered processing of the resting state connectivity patterns in important brain areas associated with pain processing. The observed pattern is completely different to healthy volunteers.

Another developing area which my team are currently working on is the measurement of blood flow in the thalamus with the use of a contrast agent. In patients with painful neuropathy, there is an increase in the vascularity of the thalamus. When this is compared with people suffering painless neuropathy, there is a delayed exit of the contrast agent. For additional comparison, healthy volunteers and normal diabetics have a rapid blood flow through the thalamus.

In the field as a whole, there is developing interest in objective measures of pain using advanced MRI. My research group has recently obtained a grant to investigate this further, to try to identify an objective marker of pain. If we are able to do this, it will be a great advance as we will be able to see the impact of drugs on the nervous system; it will provide a target to develop a new compound. This will be very interesting in the coming years as there are many areas developing in the pain assessment and brain imaging field.

There are also many unanswered questions regarding our current drugs, let alone new compounds. For example we do not know which treatment pathways (which first drug and combination treatment – as most patients will not have adequate pain relief with a monotherapy) are the most clinically effective. The more insight we can gain into current drugs and new innovative drugs the better. It is very important that we invest in these types of research to improve the quality of life of our patients.

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.

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S Tesfaye has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

- 1 Roques BP, Fournié-Zaluski MC, Wurm M. Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain. *Nat. Rev. Drug Discov.* 11(4), 292–310 (2012).
- 2 Demant DT, Lund K, Vollert J *et al.* The effect of oxcarbazepine in peripheral

neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain* 155(11), 2263–2273 (2014).