Interviews

A roundtable interview with Olivier Rascol, Toulouse University Hospital, France, and Wassilios Meissner, University of Hospital Bordeaux, France, discussed potential disease-modifying therapies for Parkinson's disease. Kailash Bhatia, University College London, UK, highlighted how newly identified Parkinson's disease biomarkers driven by AI are reshaping disease diagnosis.

Featuring: Olivier Rascol, Wassilios Meissner, and Kailash Bhatia

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Citation: EMJ Neurol. 2024;12[1]:81-86. https://doi.org/10.33590/emjneurol/LCFR6310.

Q1 Professor Rascol and Professor Meissner, what would you consider the 'turning points' that inspired you to specialise in movement disorders, particularly Parkinson's disease?

Rascol: When I started as a neurologist and a clinical pharmacologist, there were a lot of interesting developments in movement disorders, particularly Parkinson's disease, based on the understanding of the dopamine hypothesis. That was the main reason for my curiosity in this area.

Meissner: For me, it was very simple. It was, in fact, not an active choice, which I never regret. At that time, I wanted to become a neurologist at the Charity Hospital in Berlin, and the only way was to accept a position in the movement disorder group. That was how I found myself on the topic of Parkinson's disease and movement disorders.

Q2 In your opinion, what have been the most significant advancements in Parkinson's disease research over the past decade?

Meissner: The development of biological tests such as the alpha-synuclein real-time quaking-induced conversion (RT-QuIC), which one day might help us make a more accurate diagnosis.

Rascol: I would add the importance of physical exercise in disease management and a multidisciplinary approach to the management of patients.

Q3 What motivated the initiation of the Lixipark trial?

Rascol: There was a background, particularly in logical data, suggesting a link between diabetes mellitus and an increased risk of Parkinson's disease. Neuropathological studies also showed postmortem in the brain of patients with

Parkinson's disease that there were abnormalities in insulin signalling biomarkers in the substantia nigra, which is affected in Parkinson's disease. We had a mature network of French clinical research centres, which put us in a position to run academic clinical trials. Furthermore, in 2012, there was the publication of an early pilot mono-centric clinical study run by a group at University College London, UK, showing that in randomised but non-blind conditions there was a possibility of some positive effects of exenatide, another GLP1 agonist close to lixisenatide, in parkinsonian patients. This initial result was confirmed in a subsequent double- blind study conducted by the same group and published in 2017, but these results were not yet available when we started our own project. Finally, we were fortunate to be provided with the lixisenatide medication for diabetic patients at no cost by Sanofi.

Meissner: Rascol nicely summarised that there were several developments that converged to allow us to conduct this clinical trial. I would add that there was data from epidemiological studies and studies on patients with diabetes, showing, for example, that glucagon-like peptide 1 (GLP-1) receptor agonists as a whole group reduced the risk of patients with diabetes having an additional diagnosis of Parkinson's disease. There was strong evidence from the bench and epidemiological studies.

Why was lixisenatide the chosen GLP-1 receptor agonist used in this study?

Rascol: When we commenced our clinical trial study, there were not as many GLP-1 receptor agonists available and we had direct links to Sanofi who provided the drug and the placebo for the study at no cost, accounting for a large part of the trial budget. Moreover, there are not many big differences between lixisenatide and exenatide. Retrospectively, these drugs have the advantage of being relatively small molecules, which can cross the blood–brain barrier, which might not be the case for some of the more recently developed drugs. It is an advantage for targeting Parkinson's disease, a drug that is bioavailable for the brain.

> **Development of biological tests one day might help us make a more accurate diagnosis**

Q4 Can you provide an overview of the Lixipark trial and its primary objectives?

Meissner: The overall objective was to assess the effect on the progression of motor symptoms as assessed by the MDS UPS Part III scores. It was a 1-year study, where patients were randomised equally to receive lixisenatide or a placebo for a year. Overall, 156 patients were enrolled and then followed up to 14 months because there was a 12-month treatment period where we hoped that the patients would be able to continue on their stable dopamine replacement regimen, and then after 12 months there was a washout of lixisenatide and the patients were seen 2 months later. The patients were then seen off-state to get an additional potential sign of the neuroprotective effect.

Rascol: The study should be seen as a proof of concept, which is robust because the methodology is clean, it is simple, the results are straightforward, and the study is multicentric. On the other hand, we only tested lixisenatide in certain types of patients (those at an early stage of the disease only), we only followed them for a year and tested only one dose. Therefore, there are still pending questions that should be assessed in a subsequent trial before one could recommend using this drug to treat Parkinson's disease, in spite of the fact that many patients are now anxious about getting treated with the drug. Moreover, from a practical perspective, lixisenatide is not anymore available for the treatment of diabetes mellitus itself.

Q5 What were the most significant findings from the Lixipark trial, and how do they contribute to the current understanding of Parkinson's disease?

Rascol: I would say the study represents a major breakthrough because it shows that we could, with this medication, block or significantly reduce the rate of progression or worsening in severity of the motor symptoms. Furthermore, 2 months after the lixisenatide washout, the difference was still significant between the placebo and lixisenatide-treated groups, which is strongly in favour of a long-acting neuroprotective mechanism rather than a short-acting levodopa symptomatic effect. The study was well conducted, there were very few losses of follow-up and missing data. I believe that it is thanks to the quality of the centres, we train the French Network for good quality in clinical trials. Additionally, the results were consistent with what our colleagues at the University College of London, UK, reported previously in a smaller set of patients with exenatide. After 30–40 years of negative findings in the identification of neuroprotective intervention in Parkinson's disease, this is the first robust finding. Some people might comment on the fact that it was only a three-unit treatment effect on the MDS-UPDRS scale we used

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to assess disease progression, and we can discuss this aspect, but the data is the data and I believe it is unlikely to be biased. Therefore, in my view, this is an extremely important achievement after billions of dollars and decades of failures.

Meissner: You can very well imagine that based on these extremely encouraging data, we are interested in moving forward and confirming the data in a larger Phase III trial in Parkinson's disease. We are also eager to learn about the results of the Phase III trial with exenatide, and the results should be available by the end of the year. Our results have also generated significant interest in colleagues focussed more on prodromal Parkinson's disease, especially in REM sleep disorder cohorts. I had a lot of exchanges with people trying to understand how GLP-1 receptor agonists might be of interest in these early cohorts. Therefore, there really is a lot of excitement currently in the field, and we would need more clinical trials to confirm this.

Q6 Within medical research, there is significant attention being paid to the potential of GLP-1 receptor agonists to treat a variety of disorders, such as liver disease, chronic kidney disease, polycystic ovary syndrome, and disorders, such as from your research and reading. What are your thoughts on what appears to be the era of 'GLP-1 receptor agonists'?

Rascol: I understand that in Denmark, the company that is developing these compounds makes billions in profit due to the expanding use of such medications. We should not forget, however, that GLP-1 agonists can also induce some side effects, such as rare but severe pancreatitis for example. It has been shown to benefit weight loss, which is desirable for metabolic disorders, but this is sometimes ideal for patients with Parkinson's disease, who we do not want to lose weight. The mechanism of GLP-1 receptor agonists appears extremely broad and with a lot of beneficial effects in a number of pathological conditions for the brain, the kidney, blood vessels, etc. It appears like there is a big future for these drugs in medicine. At the moment, we do not recommend yet using these drugs specifically for Parkinson's disease, but this might be different for patients who have both diabetes mellitus and Parkinson's disease.

Meissner: I think it would be really important to learn more about the biological mechanisms. In Parkinson's disease, we have some pre-clinical data and there has also been some exosome-based data published in 2017, but we do not know much about the effects. There could be

some brain-related effects, but there may also be some effects on inflammation, on peripheral inflammation, on the interplay between peripheral and central inflammation, and that may be a way it operates in a variety of disorders. However, we really need to learn more about that, and we had the chance to add a couple of ancillary studies to our trial. We are currently looking for potential biological mechanisms that lead to this effect in Parkinson's disease.

Rascol: I would also like to add that it might not necessarily be appropriate to use the same dose to improve different disorders like diabetes and Parkinson's. We have been testing 20 mg/day, which is the recommended dose for diabetes mellitus, but some patients got nauseous and were allowed to reduce the dose by half to 10 mg and there was no strong evidence that the effect was less in this subgroup. Therefore, we need to further explore which is the best dose to improve and induce benefits in Parkinson's disease.

Q7 What advice would you give to young researchers interested in pursuing a career in neurology and clinical pharmacology?

Meissner: Be persistent.

Rascol: Be curious and be motivated. One of the big issues at the moment is that many young neurologists are focused on their own personal short-term quality of life, and it looks like they are less interested in making extra-efforts to be involved in research activities. I think that one needs curiosity, motivation, patience, and perseverance to enjoy work and make it exciting and rewarding.

Q8 Professor Rascol, since you were appointed head of the Toulouse Clinical Research Centre in 1994, what has been your proudest achievement, and what do you hope to accomplish in the coming years?

Rascol: First, I hope to pass down the leadership in the best way possible. Second, I think that building the Toulouse Clinical Research Centre has been an exciting achievement that allowed us to improve our knowledge on different disorders and improve our management of patients. It was also the first step to build efficient clinical research networks like the NS-Park network, without which the Lixipark trial would have never happened. I believe that in clinical research, to be efficient and creative, you need to bring together different expertise, different profiles, enough access to patients, and education to patients to test new hypotheses. If we did not have strong clinical research centres and networks, we would not have been able to conceive such a programme, run it, and have enough credibility for industry partners.

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Q9 Professor Meissner, since you were appointed head of the Department of Neurology for Neurodegenerative Diseases at the University Hospital Bordeaux, what has been your proudest achievement, and what do you hope to accomplish in the coming years?

Meissner: It has been only 4 years since I was appointed Head of the Neurodegeneration Department. I think we had the chance over the last 15 years to conduct the study because the evidence was pointing to what was going on. We have a very strong team with a lot of ideas in terms of improving patient care, so it is not only about research. From a research perspective, the Lixipark trial is my biggest achievement, and scientifically speaking it will be my greatest achievement. However, I think we need to go beyond drug development and develop a lot of complementary medicine strategies and have a holistic approach to patients and caregivers. I think this is something that we have led over the last couple of years and is something that we will continue pursuing.