Published in final edited form as:

Lancet Neurol. 2014 March ; 13(3): 237–239. doi:10.1016/S1474-4422(14)70022-5.

Rifampicin for multiple system atrophy – too little, too late?

Gregor K. Wenning, MD, PhD, MSC, Florian Krismer, MD, and Werner Poewe, MD

Department of Neurology, Innsbruck Medical University, Anichstraße 35, A-6020 Innsbruck, Austria

In the late sixties, Graham and Oppenheimer¹ were the first to recognize that olivopontocerebellar atrophy, striatonigral degeneration and the Shy-Drager-Syndrome are different presentations of the same disease which then was designated multiple system atrophy (MSA). 30 years later Niall Quinn published a seminal description² of the “*nature of the beast*” in which he, for the first time, proposed clinical diagnostic criteria for MSA. Since then, many advances in research paved the way towards a better understanding of the disease and the underlying molecular pathophysiology. This includes the extensive characterization of the natural course of the disease and the longitudinal validation of clinical rating scales which serve as foundation for the planning of clinical trials.³ In terms of research into the etiopathogenesis of the disease, one of the most intriguing finding was the observation that oligodendroglial cytoplasmic inclusions (GCI or Papp-Kahn-Lantos bodies), the subcellular hallmark feature of MSA,⁴ are mainly composed of α -synuclein.⁵ The trial by Low and co-workers, which is published in this issue of *The Lancet Neurology*, is the first to directly tackle the vicious oligodendroglial aggregation of α -synuclein.

In the present trial 100 patients were randomised to receive rifampicin or riboflavin over a period of 12 months and assessed for possible differences in progression of Unified MSA Rating Scale (UMSARS) scores and a variety of secondary outcome measures. A pre-planned interim analysis of the primary endpoint after the first 30 participants had completed the 12-month treatment period revealed that futility criteria were met and an independent Data and Safety Monitoring Board recommended the termination of the trial. There are several potential reasons why rifampicin failed to influence disease progression in MSA. Rifampicin, a bactericidal antibiotic, yielded beneficial effects in a preclinical model of MSA by reducing α -synuclein brain tissue levels through its anti-aggregenic properties.⁶ The most frequently used preclinical MSA models are characterized by oligodendroglial overexpression of α -synuclein in mice which replicates cellular hallmark features that assumingly play an important role in MSA-related pathogenic mechanisms.⁷ And it is in such models that rifampicin showed its effects.⁶ However, evidence for target engagement in such models is not necessarily predictive for disease-modifying efficacy in patients. There have been several instances where target engagement in models of neurodegenerative “proteinopathies” has not translated into clinical benefit.^{8–10} Additionally, one of the major bottlenecks for conducting disease-modifying trials in neurodegenerative movement

Corresponding Author: Prof. Gregor K. Wenning MD, PhD, MSC, Department of Neurology, Innsbruck Medical University, Anichstraße 35, A-6020 Innsbruck, Austria, Phone: (+43) (0512) 504 81811, Fax: (+43) (0512) 504 23912, gregor.wenning@i-med.ac.at.

disorders is the lack of reliable diagnostic markers for early or prodromal stages of disease. 11 Rifampicin may have the potential to successfully interfere with the aggregation of α -synuclein very early in the disease process but may fail later when, irreversible neuronal damage has set in. There are also some shortcomings of the trial itself. First, the underlying power calculation of this trial remains debatable. Due to the finding that early and advanced stage patients have different slopes of progression, the authors decided to use a combination of published natural history data¹² and their own unpublished progression rates, however, they did only partially factor disease severity into their power calculations. Second, a non-clinical surrogate marker of disease progression, e.g. imaging biomarker, would have added invaluable quantitative information on the disease progression. For instance, diffusivity changes in the putamen were shown to be sensitive to change over time in MSA patients and, thereby, provides a mean of monitoring disease progression in MSA in an objective and quantitative manner.¹³ However, there is still a critical need to refine monitoring of disease progression through α -synuclein imaging.¹⁴ Furthermore, the recruitment of Parkinson- and cerebellar-type MSA patients (1) likely introduced variability and (2), in spite of the recently observed COQ2 mutation in Japanese MSA patients (which are more likely to suffer from the cerebellar variant),¹⁵ the authors face an increased likelihood to study two pathophysiologically independent diseases.

Although the current rifampicin study has failed to demonstrate disease-modifying effects, the authors should still be commended for conducting this trial. The screening of 285 MSA patients and the recruitment of 100 eligible MSA patients in less than a year in only 10 US movement disorders centres is a major achievement and will serve as foundation for future estimations of recruitment rates for MSA trials. They also proved that stringent inclusion and exclusion criteria including the definition of maximum UMSARS are critical to reduce within-group variability of outcome measures. Similarly, it was also shown that unambiguous instructions and prior training on clinical scales such as the UMSARS considerably minimize variability. Future trials with larger sample sizes are clearly needed and should probably include biomarker outcomes to enhance the validity of the observed effects.

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