Autonomic Neuroscience: Basic and Clinical xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

Present and future of disease-modifying therapies in multiple system atrophy

Miguel Lopez-Cuina[a,b], Alexandra Foubert-Samier[a,b,c], François Tison[a,b,c], Wassilios G. Meissner[a,b,c,*]

[a] Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France
[b] CNRS, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France
[c] Centre de Référence Maladie Rare AMS, Service de Neurologie, Hôpital Pellegrin, CHU de Bordeaux, F-33000 Bordeaux, France

ARTICLE INFO

Keywords:
Treatment
Disease modifying therapies
Clinical trials
Alpha-Synuclein

ABSTRACT

Through the last decade seven clinical trials on Multiple System Atrophy have been published, virtually all of them reported negative results. Patients and family remain hopeful while facing this devastating disease, but as doctors we still cannot offer them disease-modifying therapies. The field has seen many advances regarding pathophysiology, translational research, diagnostic accuracy, natural history and imaging, but successful treatment remains elusive. This review provides an overview of the available tools for designing clinical trials, critically analyzes the past studies and describes the knowledge obtained from them, and finally gives some orientation for future trials that could meet the current needs of patients and clinicians, overcoming the hurdles met by previous studies.

1. Introduction

Multiple System Atrophy (MSA) is a rapidly progressing and fatal neurodegenerative disease characterized by a variable combination of parkinsonism, ataxia and autonomic failure (Fanciulli and Wenning, 2015; Gilman et al., 2008). The pathological hallmark is the presence of α-synuclein bearing glial cytoplasmic inclusions (GCI) (Jellinger, 2012; Papp and Lantos, 1994).

MSA is an orphan disease with an estimated prevalence ranging from 1.9–4.9/100,000 (Krismer and Wenning, 2017). Treatment is available for some symptoms, in particular autonomic dysfunction, while disease modification remains an urgent unmet need.

This review focuses on the seven randomized clinical trials (RCT) that have been completed in the last decade, six of which reported negative results. We begin by outlying the current tools available for designing a robust clinical trial fitting the characteristics of a rare disease; later we critically analyze the above-mentioned trials, inferring the possible causes of their failures to show significant results, while appraising the knowledge that can be garnered from them. Finally, we give some orientation for conceiving future RCT that could meet the current needs of patients and clinicians, overcoming the hurdles met by previous studies.

2. Diagnosis and outcomes for clinical trials in MSA

2.1. Diagnostic criteria

A first consensus statement was published in 1999 (Gilman et al., 1999), which was the standard in clinical setup and in research until the revised consensus criteria were released in 2008. The most relevant changes being related to the criteria for possible MSA with the addition of the results of paraclinical investigations, such as atrophy of the putamen, middle cerebellar peduncle (MCP), pons, or cerebellum on magnetic resonance imaging (MRI); hypometabolism on 18F–fluorodeoxyglucose positron emission tomography (FDG-PET) and presynaptic nigrostriatal denervation on single-photon emission computed tomography (SPECT) or PET (Gilman et al., 2008).

These criteria allow three levels of certainty in diagnosing MSA, possible, probable and definite. While for the diagnosis of probable MSA unequivocal signs of autonomic failure are required, the diagnosis of possible MSA allows for the use of the above–mentioned paraclinical investigations. The diagnosis of definite MSA requires post-mortem confirmation.

A study compared the performance of both consensuses in a neuropathologically confirmed cohort of 59 patients with MSA (Osaki et al., 2009). In later stages of the disease, the old and new consensus for possible and probable MSA performed similarly, with sensitivities

* Corresponding author at: Institute of Neurodegenerative Diseases, University Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France.
E-mail address: wassilios.meissner@chu-bordeaux.fr (W.G. Meissner).

https://doi.org/10.1016/j.autneu.2017.12.008
Received 31 August 2017; Received in revised form 22 December 2017; Accepted 29 December 2017

above 90%. However, differences became more apparent in earlier stages, where the new consensus criteria for possible MSA achieved a better sensitivity, albeit still remaining low (41% compared to 28%). In contrast, both consensuses showed good positive predictive values in both early and late visits (ranging from 86 to 100). This illustrates that consensus diagnosis criteria are reliable but also underscores the challenge in recruiting patients in the early phase, when clinical signs remain non-specific and interventions are believed to be more likely to modify the disease course, given that once the diagnosis becomes more obvious (often meeting criteria for probable MSA) the neurodegenerative process is in a relatively advanced stage (Gilman et al., 1999; Gilman et al., 2008). A further revision of current diagnostic criteria is warranted to improve the above-mentioned low sensibility for early-stage disease, and also to account for clinical symptoms that are increasingly being recognized. In this regard, cognitive impairment is frequent but currently considered as non-supportive feature according to consensus diagnosis criteria for MSA (Stankovic et al., 2014).

2.2. Clinical rating scales

The most frequently used outcome measure in MSA clinical trials is the Unified MSA Rating Scale (UMSARS), which has been thoroughly validated, is disease-specific, and its progression rates have been established in large natural history studies (Low et al., 2015; Wenning et al., 2013). By analyzing data from the MSA rasagiline trial, a minimally clinically meaningful decline in MSA-P was estimated to be 1.5 points on the UMSARS ADL subscale, 1.5 points on the UMSARS motor examination subscale, and 3.5 points on the UMSARS total scale, although the trial's failure to show improvement in outcome measures did not allow establishing a minimal relevant improvement, which would prove more useful at determining accurate sampling size (Krismer et al., 2016).

A prospective assessment of autonomic symptoms performed in MSA patients through the Scales for Outcomes in Parkinson's Disease–Autonomic questionnaire (SCOPA-Aut) questionnaire reported slow progression of total and subdomain scores over time, thus, not being a useful endpoint for disease-modification or neuroprotection trials (Damon-Perrière et al., 2012).

MSA health-related quality of life (Hr-QoL) has been appraised by the MSA-QoL questionnaire, the Short Form 36 Health Survey Questionnaire, the EuroQol instrument and the Parkinson's Disease Questionnaire-39 (Köllensperger et al., 2007; May et al., 2007; Miyashita et al., 2011; Schrag et al., 2006; Schrag et al., 2007; Winter et al., 2011).

Prospective studies of Hr-QoL have estimated sample sizes larger than those required by UMSARS sum scores, thus making the latter the most sensitive to change over time (Geser et al., 2006; May et al., 2007; Meissner et al., 2012). Regarding Hr-QoL in MSA, some items did not change over time probably due to the scores at baseline being already too high (e.g. difficulty with handwriting), or because some symptoms might appear in later stages of the disease (e.g. difficulty with swallowing). Given the fact that Hr-QoL measures are more and more considered as very relevant outcomes, it could prove worthwhile to revise or develop specific tools that are sensitive to change for clinical trials in MSA.

A recent study prospectively compared several clinical assessment tools (i.e. MSA-QoL questionnaire, UMSARS, Scale for the Assessment and Rating of Ataxia, Berg Balance Scale and SCOPA-Aut) during 12 months, reporting that UMSARS was the most responsive to change over time. Putting together the best responding items from all scales, they suggested a brief, 8-item scale which would require a sample size of 98 patients per group in order to detect a 30% effect with a statistical power of 90%. A limitation to the interpretation and generalizability of the results from this study is the low representation of MSA-P, given that it is less common in Japan (Matsushima et al., 2016).

It is also worth mentioning that clinical milestones are well known markers of disease progression in MSA; namely frequent falling, urinary catheterization, wheelchair dependency, dysphagia, and cognitive disability (Lee and Koh, 2012; O'Sullivan et al., 2008; Wenning et al., 2013). These could prove useful in assessing the efficacy of therapies to delay progression.

2.3. Biomarkers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention (Biomarkers Definitions Working Group, 2001). Biomarkers, especially neuroimaging, have clear potential to serve as objective endpoints for future RCT in MSA.

2.3.1. Neuroimaging

There have been interesting advances in the last decade in this field; nonetheless, it should be noted that studies have been largely performed in small cohorts, and technologies and techniques utilized vary, making it difficult to compare results and draw firm conclusions from them. Accordingly, there is a need for a joint, multicenter force in order to recruit a sufficient number of patients and follow them for, at least, one year. This would provide invaluable insights into the variability and natural history of image biomarkers in this rare disease. Beyond disease progression, imaging biomarkers for the diagnosis of MSA may be useful for patient stratification in clinical trials.

2.3.1.1. MRI. There has been an increasing interest in the use of MRI to improve the diagnostic accuracy of MSA (Brooks et al., 2009). A recent review illustrates the contribution of high field MRI and advanced MRI modalities, and their role in the diagnosis of MSA (Kim et al., 2017).

It is equally relevant to develop MRI biomarkers of disease progression to understand the underlying pathophysiology and improve patient management, as well as to monitor changes over time in RCT. Although none of the currently available MRI studies has provided a useful imaging biomarker for disease progression, numerous cross-sectional studies have shown a relation between disease severity and duration and MRI findings (Hara et al., 2016; Minnerop et al., 2007; Pellecchia et al., 2009; Tha et al., 2010; Watanabe et al., 2002). For a better understanding of the natural history of MSA, large longitudinal follow-up studies need to be conducted to provide more robust information on the correlation between MRI changes and disease progression.

Earlier studies reported a mean annual cerebral brain atrophy rate of 2.5% (3% for MSA-C and 1.9% for MSA-P) and 1.7% (Horimoto et al., 2000; Konagaya et al., 2002). Later, a whole-brain atrophy rate of 1% was reported, while regional measurements yielded annual atrophy rates of 4.5% and 3.2% in pons and cerebellum, with a correlation between infratentorial atrophy and Unified Parkinson's Disease Rating Scale (UPDRS) motor scores (MSA-P, $n = 11$) (Paviour et al., 2006). A more recent study reported a whole-brain annual atrophy rate of 1.65%, but without correlation with UPDRS motor scores (MSA-P, $n = 8$), and in a later retrospective study in 35 MSA-P and 6 MSA-C patients, this same group reported a similar annual whole-brain atrophy rate of 1.65% (Guevara et al., 2016; Guevara et al., 2017).

Utilizing voxel-based morphometry (VBM), no correlation was found between UPDRS and atrophy rates in any brain region including the striatum, mesencephalon, cerebellum, and cortex (MSA-P, $n = 14$) (Brenneis et al., 2007).

Another study reported increased atrophy rates of the cerebellum and putamen in MSA-C patients compared to healthy controls (14 MSA-C, 6 controls) (Hauser et al., 2006). Progression of atrophy has also been reported in corpus callosum and MCP (32 MSA-C, 16 MSA-P) (Minnerop et al., 2007). More recently, a retrospective study described the relation between the annual cerebellar volume atrophy rate and the increase in International Cooperative Ataxia Rating Scale (ICARS)