Parkinsonism and Related Disorders xxx (2015) 1–11

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Interventional trials in atypical parkinsonism☆

S. Eschlböck, F. Krismer, G.K. Wenning*

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

ARTICLE INFO

Article history:
Received 5 September 2015
Accepted 18 September 2015

Keywords:
Clinical trials
Multiple system atrophy
Progressive supranuclear palsy
Corticobasal degeneration
Therapies

ABSTRACT

Atypical parkinson disorders (APD) are rapidly progressive neurodegenerative diseases with a variable clinical presentation that may even mimic Parkinson's disease. Multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are commonly summarized under this umbrella term. Significant developments in research have expanded knowledge and have broadened available symptomatic treatments, particularly for the treatment of neurogenic orthostatic hypotension. Nonetheless, symptomatic support still remains limited in all of these disorders. Currently, there exists no effective treatment to delay disease progression and disease-modifying trials have failed to provide coherent and convincing results. Recent trials of rasagiline (in MSA), rifampicin (in MSA), tideglusib (in PSP) and davunetide (in PSP) reported negative results. Nevertheless, large cohorts of patients were recruited for interventional studies in the last few years which improved our understanding of trial methodology in APDs immensely. In addition, remarkable progress in basic research has been reported recently and will provide a solid foundation for future therapeutic trials. In this review, we will summarize published randomized, placebo-controlled clinical trials (RCTs) in APDs. Additionally, the design of ongoing and unpublished interventions will be presented.

1. Introduction

Atypical parkinsonian disorders comprising a heterogeneous group of tauopathies (PSP, CBD) and α-synucleinopathies (MSA) remain a challenge in diagnosis as well as in treatment. APD are characterized by a more rapid progression than Parkinson's disease (PD) and the early presence of additional debilitating symptoms including autonomic failure, gait disorders or cortical symptoms. The levodopa (L-Dopa) response is often insufficient. Although key pathogenic events remain elusive, basic research advanced the field substantially with additional knowledge being derived from cell-culture and animal models. Unfortunately, all agents that were thought to be neuroprotective in preclinical models failed to demonstrate significant disease-modifying efficacy in clinical trials. The focus of current drug therapy is on alleviating disease symptoms, which is often ineffective. In addition, treatment recommendations often residue on expert opinion as large-scale and high-quality symptomatic treatment trials are lacking. However, today we have validated rating scales and advanced neuroimaging techniques as well as international research networks at our disposal which will facilitate the conduct of future large-scale interventional trials.

In this overview, we will summarize randomized, controlled trials (RCT) of MSA, PSP and CBD with a focus on disease-modifying and symptomatic therapies. Following editorial requirements Lewy Body Dementia (DLB) will not be part of this review (see systematic review and meta-analysis Stinton et al., 2015). Motor symptoms are treated with dopaminergic therapies and patients respond well on L-Dopa treatment. The treatment of neuropsychiatric symptoms was target of numerous randomized controlled trials including treatment trials for donepezil, rivastigmine, galantamine, memantine, olanzapine, risperidone, piracetam, quetiapine, citalopram, and yokukansan. According to this meta-analysis strongest evidence for potential efficacy was provided for donepezil and rivastigmine in the treatment of cognitive and psychiatric symptoms [1].

2. Treatment options and new discoveries

2.1. α-synucleinopathy: MSA

MSA manifests in a variable clinical presentation comprising

☆ Clinical Parallel Session 3.10 Interventions in Parkinsonism (MSA/PSP/CBD) MSA 12/8/2015 8:30:00 AM–10:00:00 AM.

* Corresponding author.
E-mail address: gregor.wenning@i-med.ac.at (G.K. Wenning).

http://dx.doi.org/10.1016/j.parkreldis.2015.09.038
1353-8020/

progressive autonomic failure, parkinsonism or cerebellar symptoms. According to the predominant motor feature it can be classified in MSA-P (the parkinsonian subtype) and MSA-C (with predominating cerebellar symptoms). Oligodentroglial cytoplasmic inclusion bodies (GCIs) composed of α-synuclein represent the histopathological hallmark of this disease.

Unfortunately, evidence-based data for the treatment of motor symptoms are limited. Although patients with MSA respond poorly to L-Dopa therapy, a subgroup reports a benefit. Therefore, dopaminergic therapy is part of the symptomatic treatment strategy. Unfortunately, these recommendations are based on open-label studies and case reports due to the lack of adequate trials of dopaminergic agents. For the NMDA receptor antagonist, amantadine, a small RCT is available but its prescription is discussed controversially. The NMDA receptor antagonist in a dosage of 200 mg twice daily was assessed in 8 patients with MSA in a crossover design with a 3-week period for each treatment arm including 1 week of washout in-between. Despite of a trend towards reduction of motor symptoms, non of the outcome parameters reached statistical significance [2].

Recurrent falls due to postural instability or neurogenic orthostatic hypotension (nOH) is a common and dangerous problem. Non-pharmacological strategies to treat nOH comprise high-salt dietary, increased water intake, physical maneuvers and compression via abdominal binders and stockings. In case of severe nOH, various antihypotensive agents increasing blood volume or the peripheral vascular resistance may be helpful. Midodrine and fludrocortisone are frequently prescribed but only assessed in mixed population trials of nOH. In detail, Midodrine has been investigated in several RCTs [3–7], in patients with nOH (including MSA subjects) and is effective in ameliorating orthostatic symptoms and increasing blood pressure. Similar level of evidence is available for droxidopa (L-threo-dihydroxyphenylserine), a prodrug of norepinephrine [8,9], which has recently received further confirmation from two clinical trials. Kaufmann et al. (2014) conducted a double-blind, randomized, placebo-controlled phase 3 trial with a follow-up period of 1 week that sought to assess the efficacy of droxidopa. 162 patients (26 MSA patients) suffering from neurogenic orthostatic hypotension received droxidopa (100–600 mg/3 × d). Patients were evaluated by the Orthostatic Hypotension Questionnaire (OHQ) which included patient-reported items and standing systolic blood pressure (SBP). After 1 week droxidopa improved orthostatic symptoms and increased standing SBP [10]. In contrast, a 2-week, randomized, placebo-controlled study in 101 patients (30 MSA patients) with nOH did not meet the primary endpoint evaluated by Orthostatic Hypotension Symptom Assessment (OHSA) item 1. However, the individualized dosage of 100–600 mg three times daily improved secondary outcome measures [11]. Treatment was generally well tolerated and droxidopa was approved for symptomatic treatment of orthostatic dizziness by the FDA. Furthermore, there exists a wide range of antihypotensive drug including fludrocortisone [12,13], ephedrine [6], pyridostigmine [14,15], yohimbine [15], atomoxetine [7,16], octreotide [17] and other agents. Nonetheless, these drugs are restricted to off-label use because of lacking RCT data on efficacy and safety. Currently, there are two ongoing trials targeting orthostatic hypotension including droxidopa (NCT02071459) and pseudoephedrine/water (NCT02149901).

Supine hypertension frequently occurs in MSA and can be exacerbated by the use of antihypotensive drugs. Although RCTs in a cohort of MSA are lacking, the prescription of calcium channel blockers or nitroglycerine is common if non-pharmacological treatment is insufficient. Recently, two RCTs have been published investigating the effect of angiotensin II antagonist losartan and β_1-blocker nebivolol. In the setting of supine hypertension treatment that targets angiotensin II is not commonly prescribed. Promising effects of angiotensin II receptor antagonist losartan was demonstrated in a randomized, placebo-controlled crossover trial which assessed the contribution of angiotensin II to supine hypertension. Single dose losartan 50 mg was able to decrease overnight SBP and nocturnal urinary sodium excretion without deterioration of orthostatic symptoms the next morning. Angiotensin-converting enzyme (ACE) inhibition with captopril had no effect suggesting that formation of angiotensin II is not inevitably combined with plasma renin activity [18]. This study provides a rationale for future interventional studies for the treatment of supine hypertension in MSA. In spite of the small sample size (MSA n = 5; total n = 11) and the lack of long-term data more clinical trials are needed. Recently, a crossover clinical trial with similar design has been conducted by Okamoto et al. (2014). The effect of nebivolol 5 mg to supine hypertension was assessed in a cohort of 20 subjects including 6 MSA patients. Primary outcome was defined as decrease in SBP following β-blocker administration. In contrast to metoprolol, nebivolol lowered supine hypertension independent of β_1-blockade [19]. Concerning supine hypertension losartan 50 mg/captopril 50 mg (NCT01292694) and the endothelin blocker BQ123 (NCT01119417) are currently under investigation.

Urologic symptoms usually occur early in disease. Neurogenic bladder symptoms such as urinary urge incontinence respond to antimuscarinc treatment but possible side effects such as confusion have to be taken into consideration. Anticholinergics such as trospium chloride and oxybutynin seem to be effective in a cohort of patients with urge symptoms or incontinence. Nonetheless, trospium chloride has demonstrated a better tolerability [20]. If no amelioration is achieved botulinum toxin (BTX) injection into the detrusor muscle may be an option. Furthermore, clean intermittent self-catheterization remains first-line treatment in case of urinary retention. Alternatively, a bladder stimulator or pharmacological management with cholinergic agents or α_1-adrenoreceptor antagonists may be useful. Erectile dysfunction in men with MSA is common. The phosphodiesterase type 5 inhibitor Sildenafil is useful but orthostatic hypotension is a frequent side effect in MSA [21]. Regarding the treatment of sexual dysfunction in women no data are available.

Injection of BTX in the salivary glands is a helpful to relieve drooling and has been investigated in a cohort of MSA (n = 6) and PD (n = 14) patients in a convincing clinical trial [22]. Unfortunately, further non-motor features such as gastrointestinal symptoms, sleep disorders and neuropsychological problems have not been investigated in randomized, double-blind, placebo-controlled clinical trials.

Despite efforts in neuropathology and molecular biology disease-modifying treatments are lacking. In the past clinical trials with recombinant human growth hormone [23] and minocycline [24] failed to mediate beneficial effects. The effect of riluzole has been evaluated in a symptomatic [25] as well as in a disease-modifying trial [26], however, both trials were negative. Immunomodulation with intravenous delivery of immunoglobulins improved activities of daily life and motor scores measured by UMSARS-I and –II in a 6-months open-label trial in a small cohort of 9 MSA patients. Nonetheless, safety and tolerability remain to be established in a large RCT [27]. Currently, a phase 1 trial assessing the effect of active immunization with AFFITOPE® (PD01A or PD03A) over 1 year is running in MSA (NCT02270489). Lee et al. (2012) examined the possible neuroprotective effect of autologous mesenchymal stem cells in 33 patients with MSA-C in a randomized, placebo-controlled trial. Primary outcome measure was the change in total UMSARS after 1 year. MSC therapy could delay clinical progression and attenuated loss of cerebral glucose metabolism and grey matter density [28]. Nonetheless, safety concerns

Please cite this article in press as: S. Eschlböck, et al., Interventional trials in atypical parkinsonism, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.09.038