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Possible Treatments of Atypical Parkinsonism

Moretti Davide Vito

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Abstract

Success in treating patients with atypical parkinsonism remains exceedingly low. It is particularly important for both neurologists and general practitioners to have a guideline in the actual possible cure options. This study reviews the limited available literature reporting treatment trials about treatment in parkinsonism. Various therapeutical approaches have been tried with rasagiline, immunoglobulin, autologous mesenchymal stem cells, davunetide, lithium, and tideglusib. Recently, transdermal rotigotine (RTG) has been proposed for the treatment of atypical parkinsonism, as well as deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) alone or combined with globus pallidus internus (Gpi) stimulation. The outcomes reviewed here highlight the need for the development of randomized, placebo-controlled trials to validate outcomes about rotigotine, DBS, and all other new therapies directed at altering the underlying biological mechanisms involved in the disease process.

Keywords: atypical parkinsonism, treatment options, pharmacological intervention, deep brain stimulation, diagnosis

1. Introduction

Progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), Parkinson's disease with dementia (PDD), and dementia with Lewy bodies (DLB) are usually indicated as atypical parkinsonian syndromes (APS). Anyway, each of that syndrome is characterized by peculiar anatomic-pathological picture [1–5]. Up to date, the amount of pathophysiological data available regarding APS has progressively grown in the past two decades. Nonetheless, the etiology of APS is still under investigation and effective treatments are lacking [6,7]. Various therapeutical approaches have been tried with rasagiline, immunoglobulin, autologous mesenchymal stem cells, davunetide, lithium, and tideglu-

sib [8]. Recently, the transdermal rotigotine (RTG) has been proposed for the treatment of atypical parkinsonism [9–11], as well as deep brain stimulation of the pedunculopontine nucleus (PPN) alone or combined with globus pallidus internus (Gpi) stimulation [12]. This study reviews the limited available literature reporting treatment trials. The outcomes reviewed here highlight the need for the development of novel therapies directed at altering the underlying biological mechanisms involved in the disease process.

2. Materials and methods

This study reviews all the limited available literature reporting treatment trials about treatment in atypical parkinsonism.

3. Clinical features

Diagnosis of AP has been performed in accordance with the primary diffuse tips and medical criteria [13–20]. PSP is characterized by vertical gaze abnormalities, early falls, postural instability, and presenile cognitive impairment. PSP has two principal clinical forms: classical PSP (or Richardson's syndrome) and PSP-parkinsonism (PSP-P). Respect to the classical form, PSP-P is characterized by the presence of tremor and an inconstant clinical response to levodopa. The classical CBD phenotype includes apraxia, cortical sensory loss, alien limb, as well as dystonia and myoclonus. MSA patients usually show a mix of cerebellar and pyramidal signs, parkinsonism, and autonomic dysfunction. The predominant phenotype at onset of MSA allows the classification into MSA-parkinsonism or MSA-cerebellar form. The diagnosis of PD was made following previously published criteria [21]. Only subjects with idiopathic PD were enclosed within the present study in order to get a homogeneous sample study population [22]. So, patients had unilateral onset and development of parkinsonian signs, two of the three cardinal signs among akinesia, rigidity, and postural abnormalities and resting tremor. A superb response to a dopaminoagonist treatment was a strong criterion. In the Parkinson-dementia group, patients with idiopathic PD, who developed cognitive decline after a year of the onset of parkinsonism, were included. On the contrary, in Lewy Body Dementia (LBD) group, patients with cognitive impairment appeared within 1 year after the onset of movement disorders were included. Moreover, in this group patients with Rapid Eye Movements (REM) sleep behavior disorders, vivid dreams, hallucinations and postural instability have been enclosed [22].

4. Results

4.1. Current pharmacological chances in APS

Table 1 summarizes the most important clinical trials aiming to find a drug therapy for APS.

Authors	Disease	Treatment	Duration	Outcomes
Poewe et al. [23]	MSA	Rasagiline	48 weeks	No improvement
Novak et al. [24]	MSA	Intravenous immunoglobulin	6 months	Improvement
Lee et al. [25]	MSA-cerebellar type	Autologous mesenchymal stem cells	12 months	Improvement
Hoglinger et al. [35]	PSP	Tideglusib	12 months	Improvement
www.allontherapeutics.com, 2012	PSP	Davunetide	52 weeks	No improvement
Stamelou et al. [40]	PSP	CoQ10	6 weeks	Improvement
Moretti et al. [9–11]	MSA-PSP-CBD-LBD	Transdermal rotigotine	24 months	Improvement
Servello et al. [12]	PSP	DBS of PPN	12 months	Improvement

Table 1. Synopsis of the main clinical trials for the treatment of atypical parkinsonism.

The monoamine oxidase-B inhibitor rasagiline with the dosage of 1 mg/day has been assessed in a randomized, placebo-controlled clinical trial for 48 weeks in 174 patients with possible or probable MSA-parkinsonism type. The total Unified Multiple System Atrophy Rating Scale (UMSARS) score did not found significant improvements in the treated when compared to placebo groups [23].

A monthly infusions of 0.4 g/kg intravenous immunoglobulin for 6 months in seven patients with MSA found significantly improved UMSARS part I (activities of daily living) and II (motor functions) score. A verification study has been programmed [24] to validate the anti-inflammatory approach.

Injections of autologous mesenchymal stem cells (MSCs) in 33 patients with probable MSA-cerebellar compared with placebo demonstrated a smaller increase in total and part II UMSARS scores in the MSC group. Anyway, a careful evaluation of the exact efficacy of the staminal cells is under investigation [25].

Due to the dangers of postural instability in MSA from orthostatic hypotension, considerable attention has been directed toward blood pressure control. A synthetic norepinephrine precursor was tested in 10 patients with MSA in a randomized, double-blind, placebo-controlled study, resulting in an increase in supine and upright blood pressure [26,27]. Moreover, the droxidopa has been evaluated in a phase III clinical trial in order to assess the efficacy in orthostatic hypotension, and recently FDA approved its clinical use (<http://www.medscape.com/viewarticle/820786>). As about other autonomic symptoms, oxybutynin or tolterodine can be helpful for neurogenic bladder and desmopressin can be helpful for nocturnal polyuria, whereas sildenafil may be efficacious in erectile dysfunction, but can dramatically worsen postural hypotension (Stamelou and Bathia). Recent large controlled studies with rasagiline and rifampicin have shown no neuroprotective effect [23,28].

In regard to PSP and CBD, in clinical practice, treatment options are limited to a levodopa trial (up to 1 g/d) and amantadine for parkinsonism and gait disturbance as well as valproate or levetiracetam for myoclonus [29]. Although not sufficiently studied, botulinum toxin injections can be helpful to relieve dystonic spasms of the hand or to treat levator inhibition [30]. Early clinical trials in PSP employed drug treatment to correct alterations in the dopaminergic, cholinergic, and gamma-amino butyric acid (GABA)ergic pathways and produced limited evidence of benefit. Trials with both physostigmine and donepezil were employed with a poor response in memory as well as motor function [31,32]. As about GABAergic agonists, trials with zolpidem [33] and gabapentin [34] found, respectively, transient improvement in eye movements and inhibitory frontal function. Anyway, these trials were limited by small sample size and little evidence of a long-term benefit of the treatment.

Progressive Supranuclear Palsy Rating Scale (PSPRS) and the Schwab and England Activities of Daily Living (SEADL) did not show significant outcomes in a multinational randomized, double-blind, placebo-controlled trial in which 313 patient with PSP received davunetide 30 mg twice daily or placebo (press release December 18, 2012 by Allon Therapeutics, www.allontherapeutics.com).

The inhibitors of glycogen synthase kinase-3 (GSK-3) such as lithium or tideglusib have been administered in PSP or CBD patients in two distinct trials. The lithium trial (ClinicalTrials.gov; identifier NCT00703677) a patient with PSP ended before the natural time because the drug was not tolerated. The tideglusib trial did not show significant improvement between the high-dose, low-dose, and placebo groups in the final clinical evaluation [35].

Methylene blue derivatives are inhibitors of tau protein aggregation. These agents could be a rational treatment for PSP and CBD. Anyway, the most advanced strategies for reducing tau protein are immunologic approaches targeting different tau epitopes [36]. Moreover, passive immunization approaches, which act through anti-tau monoclonal antibody directed against various tau epitopes, were shown to block seeding activity and improve cognitive deficits in transgenic mice [37].

Microtubule-stabilizing agents are also explored as potential therapies compensating the loss of tau protein function in PSP and CBD. In particular, taxanes, a class of cancer drugs and a related class of compounds called epothilones, are now being investigated as tau-related neurodegeneration. The epothilone D was found to improve axonal microtubule density and improved spatial learning in treated mice [38,39]. It has been suggested that mitochondrial dysfunction may contribute to pathogenesis of atypical parkinsonisms. This evidence has led to an interest in replacing the coenzyme Q10 (CoQ10), a component of the complex I of the mitochondrial chain. A small, double-blind, placebo-controlled, randomized trial involving 21 PSP patients treated with CoQ10 for 6 weeks has shown improvement in PSPRS scores, frontal assessment battery scores, and occipital energy when compared with placebo [40]. Currently, a large phase III trial with CoQ10 in PSP patients for 12 months is underway.

As about the LBD, the cholinergic deficit that affects in an important way these patients could benefit from the cholinesterase inhibitors; hallucinations, neuropsychiatric symptoms, and psychosis are all reduced in LBD [41].

In a large, randomized, double-blind controlled trial with 120 LBD patients over 20 weeks, rivastigmine treatment resulted in reduction of apathy, delusions, anxiety, and hallucinations, as well as improvements in cognitive assessment [42]. Furthermore, a 3-week post-treatment follow-up has also shown better Neuropsychiatric Inventory (NPI) scores [43]. A recent multicenter trial in Japan has administered donepezil to 140 patients with LBD showing clinical, cognitive, and behavioral improvement when compared to placebo [44].

Recently, the effect of memantine, an NMDA-receptor antagonist, has been evaluated in two clinical trials [45,46] in patients with both LBD and PDD. Although some clinical benefits have been reached, the effect of memantine remains inconclusive.

Atypical antipsychotic agents such as quetiapine are recommended because of the risk of extrapyramidal side effects in patients with LBD. Clonazepam at low dosage could be used in REM sleep behavior disorder. As about parkinsonian disorders, levodopa should be administered instead of dopaminergic agents with a particular care to the aggravation of psychotic symptoms.

4.2. Transdermal RTG as treatment option for atypical parkinsonian syndrome

Transdermal RTG seems to be effective and well tolerated in patients with APS. Recent studies [9–11] show significant improvement in UDPRS-III scores, maintained along the course of the 248 months follow-up. Only seven patients were dropped out, and 15 patients were affected by adverse events. In this study, behavioral or psychiatric adverse events and ICDs were not found. Moreover, results also show a reduction in NPI scores that became significant at the last follow-up evaluation (T18). Finally, during the study the patients did not suffer from congestive heart failure. These results confirm previous evidences obtained in patients with idiopathic Parkinson's disease showing positive effect on motor control and behavioral disturbances [47–55] as well as a good safety of RTG [56]. On the whole, these outcomes highlight that transdermal RTG should be considered as a therapeutic option for the treatment of atypical parkinsonism.

4.3. Deep brain stimulation in PSP

In a recent study [12], three patients with PSP were submitted to the deep brain stimulation of the pedunculopontine nucleus (PPN). A reduction of falls and an amelioration of postural balance were observed. The patients required less assistance for daily living activities. The clinical improvement was, however, not fully reflected in the evaluating scales. The mean PSPRS percentage decrease was of 26.3% (SD = 8.3) at the 12-month follow-up visit for the three patients. The diversity between the reported improvement and the PSPRS might be due to the phenomenological diversity of PSP, not fully captured by the PSPRS, and repeated scheduled postoperative evaluations are necessary to capture objectively the overall clinical improvement. That the greatest PSPRS percentage decrease (35.7%) was seen in the double-implanted GPi-PPN patient is possibly due to the improvement of the concomitant amelioration of his or her dystonic state. It remains of course speculative in light of a single case if this better clinical outcome seen in the GPi-PPN patient is reflection of an increased synergic effect

of PPN and GPi secondary to stimulation, bearing in mind the strong connectivity between the basal ganglia and the PPN. An interesting observation was related to the stimulation parameters; we started with low-frequency stimulation, which was increased progressively to 130 Hz without noticing a significant change in clinical presentation.

4.4. Supportive therapies

The palliative therapies are highly recommended in APS patients. An assortment of physical, occupational, and language therapies should be considered, paying attention to the most invalidating symptom, that is, apraxia. If the risk of falls and postural instability become prevailing symptoms, a wheelchair has to be suggested and should be advised to patient and family. This acknowledgment can be shockingly testing and troublesome. Numerous families see the utilization of a wheelchair as a marker of the last loss of the capacity to ambulate and stay free. They should be persuaded that in addition to the fact that this is vital for the well-being of the patient, the wheelchair can give a more prominent level of flexibility than the constrained portability given by the patient's attempts to try to deambulate. At long last, it is vital to screen and support the prosperity of the caregivers. The especially troublesome mix of serious motor inability with cognitive and behavioral aggravations increases the risk of an overwhelming burnout.

4.5. Future treatment options

Different approaches such as "regenerative" or "restorative" (e.g., stem cells and trophic factors) are desirable to provide advance in the field of disease-modifying therapy. Trials of "neuroprotective" therapies are actively being planned or have been implemented (e.g., a trial of riluzole for PSP and multiple system atrophy has been initiated in Europe). Further discussion and evaluation of the best endpoints for clinical trials in these disorders are an important priority. One of the major obstacles to the design of the necessary clinical trials is the accuracy of clinical diagnosis. This finding emphasizes the need for developing biological markers for these neurodegenerative disorders. The similarities in the underlying neuropathology and molecular biology of these disorders suggest that critical advances in this field will equally impact on the treatment outcomes [1].

5. Conclusions

Up to date, the possibilities of the APS care are without no doubt very low. Two main goals are to achieve: the better understanding of the pathogenic mechanisms and the improvement of both symptomatic and disease-modifying treatments through controlled clinical trials. In the near future, every effort should be made to give hope to patients and caregivers whose number will not decrease.

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Author details

Moretti Davide Vito

Address all correspondence to: davide.moretti@afar.it

IRCCS S. Giovanni di Dio Fatebenefratelli, Brescia, Italy

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