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REVIEW

Recent Advances in Clinical Trials in Multiple System Atrophy

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Abstract

Purpose of Review This review summarizes previous and ongoing neuroprotection trials in multiple system atrophy (MSA), a rare and fatal neurodegenerative disease characterized by parkinsonism, cerebellar, and autonomic dysfunction. It also describes the preclinical therapeutic pipeline and provides some considerations relevant to successfully conducting clinical trials in MSA, i.e., diagnosis, endpoints, and trial design.

Recent Findings Over 30 compounds have been tested in clinical trials in MSA. While this illustrates a strong treatment pipeline, only two have reached their primary endpoint. Ongoing clinical trials primarily focus on targeting α-synuclein, the neuropathological hallmark of MSA being α-synuclein-bearing glial cytoplasmic inclusions.

Summary The mostly negative trial outcomes highlight the importance of better understanding underlying disease mechanisms and improving preclinical models. Together with efforts to refine clinical measurement tools, innovative statistical methods, and developments in biomarker research, this will enhance the design of future neuroprotection trials in MSA and the likelihood of positive outcomes.

Keywords Multiple system atrophy · Clinical trials · Disease-modifying therapies · Alpha-synuclein

Introduction

Multiple system atrophy (MSA) is a rare neurodegenerative disease characterized by parkinsonism, cerebellar symptoms, and autonomic dysfunction to various extents [1]. The neuropathological hallmark is the accumulation of alpha-synuclein (aSyn) aggregates in oligodendrocytes known as glial cytoplasmic inclusions (GCIs) but also neuronal deposits in smaller proportions [2]. These histopathological features contributed to the classification of MSA as a synucleinopathy, together with dementia with Lewy bodies (DLB) and Parkinson's disease (PD). The average survival rate is 6–10 years after symptom onset [1–3]. No effective treatment can significantly alleviate symptoms or slow disease progression in MSA. Although the precise relation between aSyn accumulation and neural death is incompletely understood, the aggregation of native aSyn is believed to contribute to numerous cellular dysfunctions in MSA [4, 5]. GCIs correlate with cell loss and regional brain atrophy [6, 7]. GCIs-aSyn strains further differ from those in other synucleinopathies and show distinct seeding patterns [8, 9•,

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10•]. Altogether, targeting aSyn is currently considered the most promising strategy for neuroprotective trials in MSA.

This review summarizes previous and ongoing neuroprotection trials in MSA (Fig. 1). It also describes the preclinical therapeutic pipeline and provides some considerations relevant to successfully conducting clinical trials, i.e., diagnosis, endpoints, and trial design.

Diagnosis, Endpoints, and Trial Design

Neuroprotection trials usually rely on patients in the earliest disease stages, while the diagnosis of MSA may be challenging within the first years. The 2008 consensus diagnosis criteria defined two clinical categories, possible and probable MSA [11••]. Their limited sensitivity to detect early-stage patients led to a recent revision [12–14]. According to a post-mortem exercise, the revised criteria show improved sensitivity at earlier stages while maintaining high specificity [15•].

The Unified Multiple System Atrophy Rating Scale (UMSARS), introduced in 2004, is the most specific metric for assessing symptom severity and progression [16]. It has been used as the primary endpoint in almost all recent randomized clinical trials, while acknowledged limitations have led to an ongoing revision [17••]. For instance, some UMSARS items imperfectly correlate with disease progression or do not reflect the patient's perspective [18]. In other words, each item may have a different informative contribution to progression changes. Recent efforts to address this limitation have resulted in the proposal of several abbreviated scales. Based on a 9-item subset, one aimed to provide a more patient-centered approach and demonstrated adequate psychometric properties [19, 20]. Two other versions adopted a data-driven approach; one used the mean standardized difference for each item after 1 year of progression [21], while the other employed an Item Response Theory (IRT) model with measurements taken at multiple time points [22]. IRT allows computing the percentage of information each item carries to explain an underlying construct, for example, disease severity. Thus,

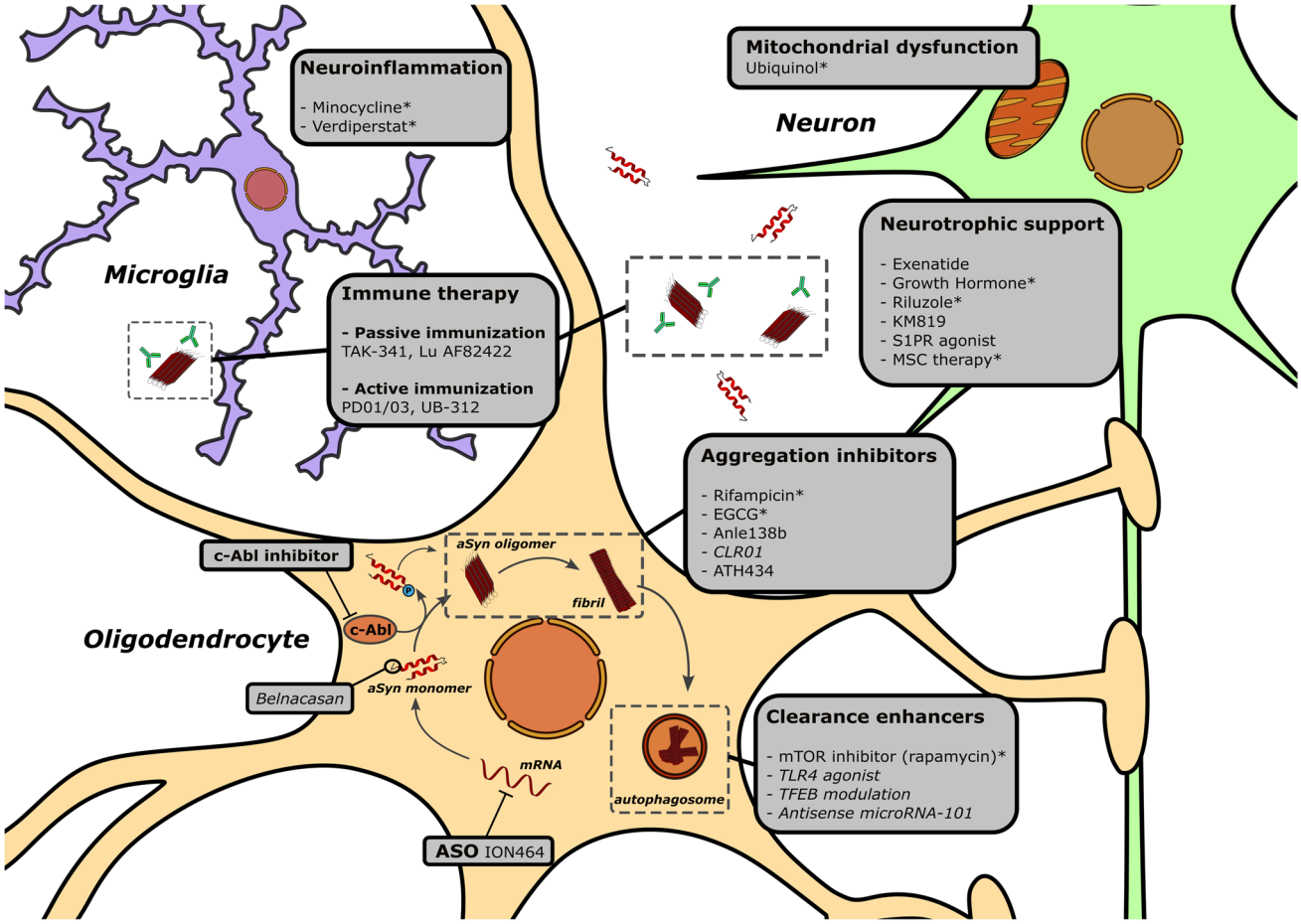

Fig. 1 Illustrated summary of tested compounds and their supposed therapeutic target at the cellular level. Compounds written in italics are currently in the preclinical development stage. Completed trials are indicated by an asterisk

IRT could help identify better-suited subsets of items for describing the latent variable. Both approaches mentioned above yielded an 11-item scale despite differences in item selection [21, 22]. Although these initiatives reflect preliminary work, they provide evidence that selecting a subset of UMSARS items is a valuable strategy to reliably detect changes in disease progression.

Additional challenges are the rarity (limiting the number of available patients for enrollment) and the aggressiveness (substantial risk of loss to follow-up due to death) of MSA, demanding adapted statistical planning. While large-scale natural history cohorts have provided significant data on progression rates, these may have inadequately addressed the issue of missing data across longitudinal observations. This could introduce potential biases, particularly as surviving patients may exhibit a slower rate of disease progression. More suited statistical approaches like joint modeling may better estimate patients' trajectories [23, 24]. In brief, joint models simultaneously analyze the time-varying, longitudinal data (e.g., UMSARS score) and the potentially associated time-to-event (e.g., time-to-death). Along the same line, estimating sample sizes and testing for primary endpoints in clinical trials should consider progression and dropout rates precisely. Classical approaches such as the Student's *t*-test only consider the difference between two observed time points (e.g., the change of UMSARS scores over a year), i.e., the same number of observations between the two time points are required. Conversely, linear mixed models (LMM) can exploit additional information (e.g., intermediate UMSARS measures, exact time of the study visit), and handle incomplete follow-up, allowing better precision, which eventually is likely to reduce the necessary sample sizes.

By leveraging data from the French MSA cohort, we compared classical Student versus LMM for sample size determination using UMSARS sum scores based on the item combinations cited above. We extracted from our cohort a population that fulfills the common criteria for inclusion in clinical trials, that is, (1) symptom onset ≤ 4 years at first visit and (2) the absence of severe impairment of speech, swallowing, and walking as markers of advanced disease. Our simulations illustrate that using LMM instead of a Student's *t*-test leads to a substantially smaller sample size. In contrast, decreasing the number of UMSARS items leads to higher required sample sizes (Table 1). Finally, the sample size increases with the data-driven subscales [21, 22] are almost negligible.

Finally, to increase diagnosis performance and precision of meaningful endpoints, there is a crucial need to incorporate biological markers reflecting the underlying disease mechanisms. To this extent, neuroimaging features have been added to the revised diagnostic criteria for MSA, and algorithms based on automated categorization may further enhance diagnostic accuracy in the future [25, 26]. More recently, a PET tracer for aSyn showed promising results in detecting specific MSA pathology compared to PD patients [27•]. Similarly, fluid biomarkers hold strong potential to improve diagnostic accuracy. In this line, increasing evidence suggests that aSyn seeding amplification assays allow the distinction between MSA and Lewy body disorders with high precision [9•, 28•, 29]. Moreover, recent studies have highlighted the potential of additional biomarkers. For instance, neurofilament light chain (NfL) blood and

Table 1 Power calculation using UMSARS-1, 2, total UMSARS, and modified UMSARS (1 + 2) scores. Modified UMSARS scores are based on - Potashman et al. [18, 19]. Scale 1 includes UMSARS-1 items 1, 4, 5, 6, 7, 10 and UMSARS-2 items 11, 12, 14. Scale 2 includes the same items as scale 1, but 0 and 1 scores were collapsed into one score. Scale 3 includes the same items as scale 1 minus UMSARS-1 item 10. - Foubert et al. [21], UMSARS-1 items 1, 4, 5, 6, 7 and UMSARS-2 items 2. - Palma et al. [20], UMSARS-1 items 2, 3, 6, 7, 11 and UMSARS-2 items 1

Effect size		30%		40%		50%	
Test		Student	LMM	Student	LMM	Student	LMM
Potashman et al.	Scale 1	136	101	76	55	49	36
	Scale 2	159	116	89	64	57	40
	Scale 3	137	101	77	56	49	35
Foubert et al.		123	89	69	50	44	31
Palma et al.		118	86	66	48	43	30
UMSARS-1		144	115	81	63	52	40
UMSARS-2		164	123	92	68	59	43
Total UMSARS		109	82	61	46	39	28

We considered a 5% type 1 error, 80% power. In mixed analysis measures, 5 measures were considered with a total of 10% dropout rate (+1% at each visit). Initial parameters were calculated by considering the following subset of the French MSA Cohort: (1) delay since MSA symptom onset ≤ 4 years and (2) UMSARS 1 item 1, 2 and 7 score ≤ 3. All visits within 1.5 years from first visit were considered. *UMSARS* Unified Multiple System Atrophy Rating Scale, *LMM* linear mixed model

cerebrospinal fluid (CSF) levels may help distinguish MSA from other synucleinopathies and predict disease severity and progression in MSA [30, 31]. These advances will likely improve patient selection and stratification in future clinical trials.

Targeting Alpha-Synuclein

The following sections will highlight the attempts to target aSyn in humans and the preclinical pipeline of potential future compounds. These are summarized in Tables 2 and 3, respectively.

Reduction of Expression

Antisense oligonucleotides (ASO) modulate targeted gene expression [60]. This technology is tested on neurodegenerative diseases, such as amyotrophic lateral sclerosis and Huntington's disease (HD). For instance, trials assessing ASO in HD failed to provide evidence for efficacy [32, 33]. In addition, a safety warning emerged in a phase 3 trial because of increased cerebrospinal fluid NfL levels and time- and dose-dependent expansion of ventricle volume in treated patients.

ASO targeting the mRNA of the *SNCA* gene that codes for aSyn reduced endogenous aSyn expression and pathology in several preclinical models of PD [34, 61, 62]. It also restored behavioral and cognitive functions [35, 36] and mitigated neural loss [61–63]. In another study using a transgenic mouse model of PD, the reduction of aSyn expression by ASO restored dopaminergic neurotransmission deficits but failed to provide behavioral improvement [64]. Furthermore, treated animals in one study showed behavioral deficits, such as altered motor coordination, reduced food intake, and impaired sleep [62]. These findings raise potential safety concerns about therapeutic approaches reducing the genetic expression of aSyn due to possible interference with its physiological roles [65]. A phase 1 study on healthy subjects and MSA patients with the ION464 compound started in July 2022 (NCT04165486).

Immune Therapy

Passive Immunization

Two monoclonal antibodies targeting aSyn are currently being assessed in MSA, i.e., TAK-341 and Lu AF82422. Both compounds are supposed to bind to aggregated isoforms of aSyn while more effectively inhibiting the formation of aSyn oligomers [39]. While these molecules were primarily evaluated in animal models of PD, there is also evidence that passive immunization strategies induce aSyn clearance in transgenic models of MSA [37, 66]. TAK-341 (formerly MEDI1341) prevented aSyn accumulation and neural propagation in mice models using lentiviral vector-mediated overexpression of aSyn [38]. Phase 1 studies on healthy subjects (NCT03272165) and PD patients (NCT04449484) provided evidence for safety and dose-dependent target engagement [67]. Lu AF82422 was well tolerated in naive animals, healthy humans, and patients with PD [68, 69]. Both compounds are currently evaluated in phase 2 studies in MSA patients (NCT05526391, NCT05104476).

Another strategy combines immunization (CD5-5) with an anti-inflammatory agent (lenalidomide). This combination attenuated behavioral deficits and reduced aSyn levels, astrogliosis, and microgliosis in transgenic MSA mice [66]. This strategy has yet to be implemented in studies in humans.

Active Immunization

Active immunization may be therapeutic by requiring less frequent administration than passive immunization. One concern in the past has been cross-reactivity and T-cell-mediated toxicity [70]. Recent advances in the bioengineering of antigenic candidates have allowed the overcoming of these limitations by producing neo-epitopes inducing a specific humoral response while preventing T-cell activation [40]. When tested in transgenic PD, LBD, and MSA models, the neo-epitope AFF1 generated sustained plasma levels of IgG against aSyn oligomers and targeted both intracellular and axonal aSyn. AFF1 effectively mitigated neurodegeneration and behavioral deficits in these preclinical models [71–73].

The two epitope variants PD01 (corresponds to AFF1 in preclinical studies) and PD03 were evaluated in phase 1 studies in patients with PD and MSA. All studies showed a good safety profile, and both compounds induced antibodies against the immunizing peptide and, to a lesser extent, against the alpha-synuclein epitope, with reactivation after booster injections [74, 75]. When tested in MSA patients, PD01 induced higher antibody titers against aSyn than PD03, and both compounds were well tolerated except for transient injection-site reactions [76]. As expected, the number of adverse events was higher than those observed in PD patients due to the overall severity of MSA compared to PD. Notably, none of the studies reported a neuroinflammatory event. More recently, another immunizing peptide targeting specifically oligomeric and fibrillar aSyn (UB-312) was tested on healthy subjects. It induced anti-aSyn antibodies in CSF and showed a good safety profile [77]. Further development includes enrolling patients with PD, MSA, and LBD in a phase 1/2 study ([78], NCT05634876).

Table 2 Completed and ongoing clinical trials in MSA

Therapy	Number of patients	Presumed mechanism of action	Phase	Design	Primary endpoint (secondary endpoint)	Status/results	Reference/NCT identifier
Compounds targeting aSyn							
ION464	30	Reduction of aSyn expression through an antisense oligonucleotide	I	RCT	Safety, tolerability (change of CSF aSyn levels, plasma, and CSF pharmacokinetic profiles)	Recruiting	NCT04165486
TAK-341	138	Passive immunization against aSyn	II	RCT	Change in a modified UMSARS Part I at 12 months (change in part I, II and total UMSARS, CGI-I, SCOPA-AUT, OS)	Recruiting	NCT05526391
Lu AF82422	64	Passive immunization against aSyn	II	RCT	Change in total UMSARS at the end of treatment from 48 to 72 weeks (change in UMSARS I, II, IV, SE-ADL, CGI-S, PGI-S, OGI-S, COMPASS, EQ-5D-5L, brain volume in volumetric MRI, NfL levels in CSF, plasma and CSF pharmacokinetic profiles)	Active, not recruiting	NCT05104476
PD01/03	30	Active immunization against toxic α-synuclein forms	I	Patient + examiner blind	Safety and tolerability, immunogenicity against α-synuclein	Safe and well tolerated, PD01 induced immune response against α-synuclein	[76]
UB-312	8	Active immunization against α-synuclein	I	patient blind	Changes in plasma and CSF levels of aSyn antibodies	Recruiting	NCT05634876
Rifampicin	100	Inhibition of formation of α-synuclein fibrils	III	RCT	Change in UMSARS I score at 12 months (change in UMSARS I, II and total, COMPASS-select at 12 months)	Study prematurely terminated, ineffective	[80]
Epigallocatechin gallate (EGCG)	92	Inhibition of α-synuclein aggregation	III	RCT	Change in UMSARS II score at 12 months (exploratory assessment of MRI parameters)	Ineffective	[41]

Table 2 (continued)

Therapy	Number of patients	Presumed mechanism of action	Phase	Design	Primary endpoint (secondary endpoint)	Status/results	Reference/NCT identifier
ATH434	60	Reduction of oxidative stress, inhibition of aSyn aggregation	II	RCT	Change in iron content in brain MRI at 12 months (change in UMSARS, SF-36, CSF NfL light chain and aggregated aSyn levels)	Recruiting	NCT05109091
Sirolimus	47	Increase of aSyn autophagy through mTOR pathway inhibition	II	RCT	Change in UMSARS at 48 weeks (exploratory analysis on putaminal volume and diffusivity, whole brain volume, plasma NfL and aSyn levels, retinal OCT)	Ineffective in a futility analysis. No significant clinical and biomarker effect	NCT03589976
Other approaches							
Riluzole	404	Anti-excitotoxic activity, free-radical scavenging	III	RCT	Survival (rate of decline in motor function)	Ineffective	[94]
Rasagiline	174	MAO-B inhibitor	II	RCT	Change in total UMSARS score at 48 weeks (change in CGI-I, COMPASS-select, and MSA-QoL at 48 weeks, change in total UMSARS II at 24 weeks; Putaminal diffusivity was assessed in ancillary imaging study)	Ineffective	[103]
Safinamide	49	MOA-B inhibitor	II	RCT	Safety and tolerability at 12 weeks (change in UMSARS II, MSA-QoL, MoCA, UDRS, goniometric measurements)	Completed	NCT03753763
Growth hormone	43	Pro-survival effects	II	RCT	Total UPDRS score and autonomic tests at 6 and 12 months (total UMSARS score at 6 and 12 months)	Ineffective, high dropout rate	[58]

Table 2 (continued)

Therapy	Number of patients	Presumed mechanism of action	Phase	Design	Primary endpoint (secondary endpoint)	Status/results	Reference/NCT identifier
Minocycline	63	Inhibition of microglial activation	III	RCT	Change in UMSARS II score at 48 weeks (change in UMSARS I, III, UPDRS III, SF-12, and EQ-5D at 48 weeks; specific PET binding for microglial activation was assessed in small ancillary study, *n*=8)	Ineffective (reduced microglial activation on PET in ancillary study)	[54]
Intravenous immunoglobulins	9	Reduction of inflammatory process	II	OL	Safety and tolerability (change in UMSARS part I and II, changes in MRI parameters)	Increase of systolic blood pressure, drop-outs due to skin rash, improvement of UMSARS I and II. No changes in brain MRI analysis	[56]
MSC delivery (intra-arterial and intravenous)	33	Neurotrophic effects, neural cell differentiation	II	RCT	Change in total UMSARS score at 12 months (change in UMSARS II score and imaging outcomes at 12 months)	Smaller increase in total UMSARS score (smaller increase in UMSARS II score and positive effects on imaging outcomes), safety concerns (ischemic MRI brain lesions in one-third)	[100]
Fluoxetine	81	Serotonin reuptake inhibition, increased neurotropic support	II	RCT	Change in total UMSARS at 3 months (change in SCOPA-Aut, BDI, MSA-QoL, SF-36, change in total UMSARS at 6 months)	Ineffective. Small decrease in UMSARS part II and emotional/social subscale of MSA-QoL	[96]
Intrathecal MSC delivery	24	Neurotrophic mediation, neural cell differentiation	I/II	OL	Frequency and type of adverse events (change in total UMSARS and indices of autonomic failure at 12 months)	Safe and well tolerated, except for low back/leg pain, associated with thickening of lumbar nerve roots in the highest-dose group, slower rate of UMSARS progression compared to placebo group of rifampicine RCT (see above)	[101]

Table 2 (continued)

Therapy	Number of patients	Presumed mechanism of action	Phase	Design	Primary endpoint (secondary endpoint)	Status/results	Reference/NCT identifier
Intrathecal MSC delivery	76	Neurotrophic mediation, neural cell differentiation	II	RCT	Change in total UMSARS at 1 year (Change in UMSARS I, II, modified UMSARS, COMPASS, rate of MRI atrophy of selected brain regions at one year)	Recruiting	NCT05167721
AZD-3241 (verdiperstat)	58	Myeloperoxidase inhibition	II	RCT	Safety and tolerability, striatal change in PET binding for microglial activation	Safe and well tolerated, no change in [11C]PBR28 binding.	[59]
BHV3241 (verdiperstat)	336	Myeloperoxidase inhibition	III	RCT	Change in a modified UMSARS score at 48 weeks (change in UMSARS I II, CGI-I, MSA-QoL)	Ineffective	NCT03952806
Ubiquinol	140	Coenzyme Q10 supplementation	II	RCT	change in UMSARS part II at 48 weeks (changes in UMSARS part I, Barthel index, SARA, walking distance, plasma ubiquinol levels)	Reduced UMSARS II progression	[57]
Exenatide	50	Glucagon-like peptide-1 agonist	II	OL	Change in total UMSARS at 48 weeks (MSA-QoL, loss of independent ambulation, number of falls, frequency of speech/swallowing impairment, CGI, MoCA)	Active, recruitment completed	NCT04431713
Inosine 5'-monophosphate	43	Increase of urate levels. Reduction of oxidative stress	II	RCT	Safety, tolerability, and target engagement: serum uric acid elevation at 6 months (changes in total UMSARS, MMSE, MoCA, GDS)	Good safety and tolerability. Significant rise of uric acid.	[126]

Table 2 (continued)

Therapy	Number of patients	Presumed mechanism of action	Phase	Design	Primary endpoint (secondary endpoint)	Status/results	Reference/NCT identifier
KM-819	78	Inhibition of FAF1 and Fas1-mediated apoptosis	II	RCT	Change in putaminal DAT binding in PET imaging at 36 weeks (change in total UMSARS, UMSARS part I and II, UPDRS III, SARA, MoCA, BDI, change in putaminal and cerebellar FDG-PET binding, safety and tolerability, pharmacokinetics)	Recruiting	NCT05695378
ONO-2808	80	S1PR agonist. Neurotrophic modulation	II	RCT	Safety and tolerability, pharmacokinetics	Recruiting	NCT05923866

BDI, Beck Depression Inventory; CGI-S *and I*, Clinical Global Impression-Severity and Improvement; *COMPASS*, Composite Autonomic Symptom Score; *CSF*, Cerebrospinal fluid; *GDS*, Geriatric Depression Scale; *MMSE*, Mini-Mental State Examination; *MoCA*, Montreal Cognitive Assessment; *MRI*, Magnetic Resonance Imaging; *FDG*, FluoroDesoxyGlucose; *MSA-QoL*, Multiple System Atrophy Health-related Quality of Life; *MSC*, Mesenchymal Stem Cells; *NfL*, Neurofilament light chain; *OCT*, Optical Coherence Tomography; *OGI-S*, Observer-Reported Global Impression - Severity; *OL*, Open label; *OS*, Overall Survival; *PET*, Positron Emission Tomography; *PD*, Parkinson Disease; *RCT*, Randomized Placebo-Controlled Trial; *SARA*, Scale for the Assessment and Rating of Ataxia; *SCOPA-Aut*, SCales for Outcomes in Parkinson's disease-Autonomic; *SE-ADL*, Schwab and England Activities of Daily Living; *SF-12/36*, Short-Form Survey 12/36; *UDRS*, Unified Dystonia Rating Scale; *UPDRS*, Unified Parkinson's Disease Rating Scale; *UMSARS*, Unified Multiple System Atrophy Rating Scale

Table 3 Preclinical treatment pipeline

Compound	Target	Mechanism	Outcomes	Model [reference]
ION464	aSyn mRNA	Antisense Oligonucleotide	Protection of nigral and hippocampal neurons ⇩ aSyn expression ⇩ aSyn burden ⇩ motor function ⇩ body weight	Wild-type mice [32] Induced aSyn phenotype in wild-type mice [33, 34] Transgenic mouse models of PD [35, 36]
TAK-341/MEDI1341	aSyn	Passive immunization	⇩ aSyn accumulation and propagation	Lentiviral-based in vivo mouse model of aSyn [37]
Lu AF82422	aSyn	Passive immunization	⇩ free aSyn in plasma ⇩ free/total aSyn ratio in CSF	Cynomolgus monkey [38]
CD5-D5 and lenalidomide	aSyn and immunomodulation	Passive immunization, T cell co-stimulation, ⇩TNFα	⇩ astroglial and microglial activation ⇩ aSyn burden ⇩ hyperactivity phenotype	Transgenic mouse model of MSA [39]
AFF1 (corresponds to PD01 in clinical trials)	aSyn	Active immunization	Protection of striatal and cortical neurons Induction of anti-aSyn antibodies ⇩ aSyn burden ⇧ microglial activation ⇧ myelination ⇧ motor function	Transgenic mouse model of MSA [40]
ATH434/PBT434	aSyn Oxidation states of iron	Aggregation inhibitor, ion metals chelation	Protection of nigral neurons ⇩ aSyn burden ⇩ oxidative stress ⇧ motor function	Transgenic mouse model of MSA [41, 42] Induced and transgenic mouse models of PD [43]
Anle 138b	aSyn	Aggregation inhibitor	Protection of nigral neurons ⇩ aSyn burden ⇩ microglial activation ⇧ motor function	Transgenic mouse models of MSA [44] and PD [45]
CLR01	aSyn	Aggregation inhibitor	Protection of nigral neurons ⇩ aSyn burden ⇩ anxiety-like behavior	Transgenic mouse model of MSA [46] Induced and transgenic mouse models of synucleinopathy [47]
Belnacasan	aSyn	Inhibition of C-terminal truncation by caspase-1	Protection of nigral neurons ⇩ truncated aSyn ⇩ aSyn burden ⇧ motor function	Transgenic mouse model of MSA [48]
TFEB	aSyn	Autophagy enhancer	Protection of nigral neurons ⇩ aSyn burden ⇧ neurotrophic support ⇧ autophagy	Induced rat model of PD and transgenic mouse model of MSA [49]
Monophosphoryl lipid A	TLR4	TLR4 agonist Inducer of phagocytosis	Protection of nigral and striatal neurons ⇩ aSyn burden ⇧ motor function	Transgenic mouse model of MSA [50]
Antisense microRNA-101	Gene regulating autophagy expression	antisense microRNA	⇩ oligodendrial aSyn ⇧ autophagy	Transgenic mouse model of MSA [51]
Kallikrein-6	aSyn	Cleavage	Protection of striatal neurons ⇩ aSyn burden ⇧ myelination ⇩ hyperactivity phenotype	Transgenic mouse model of MSA [52]

Table 3 (continued)

Compound	Target	Mechanism	Outcomes	Model [reference]
YTX-7739	Stearoyl-CoA Desaturase	modulation of aSyn conformations and membrane interactions	⇩ aSyn toxicity	neurons derived from human induced pluripotent stem cells [53]
Benztropine	Myelin	Muscarinic antagonist	Protection of cortical neurons ⇧ myelination	Transgenic mouse model of MSA [54]
Exenatide	Insulin resistance	Glucagon-like peptide-1 analogue	Protection of nigral neurons ⇩ aSyn burden ⇩ insulin resistance	Transgenic mouse model of MSA [55]
Sodium phenylbutyrate	Histone deacetylase	Histone deacetylase inhibition	Protection of nigral neurons ⇩ aSyn burden ⇧ motor function	Transgenic mouse model of MSA [56]
KM-819	FAF1	Inhibition of the FAF1 pathway Reduction of neural cell death	Neurorestorative effects in striatal dopamine neurons	Induced mouse model of PD [57]
FTY720-Mitoxy	Sphingosine-1 phosphate receptors	Increase of neurotrophic factors	⇩ aSyn burden ⇩neuroinflammation ⇧ neurotrophic factors ⇧ mitochondrial function ⇧ motor function	Transgenic mouse model of MSA [58]
Epsin2	FABP7/aSyn hetero-aggregates	Regulation of aSyn aggregates	⇩ aSyn burden ⇧ motor function	Transgenic mouse model of MSA and induced aSyn aggregation in wild-type mice [59]

aSyn, α-synuclein; *CSF*, cerebrospinal fluid; *FABP7*, fatty acid-binding protein7; *FAF1*, Fas-Associated Factor 1; *MSA*, multiple system atrophy, *PD*, Parkinson's disease; *mRNA*, messenger ribonucleic acid; *microRNA*, microribonucleic acid; *TLR4*, Toll-like receptor 4

Aggregation Inhibitors

Rifampicin was the first drug tested in MSA patients for its potential anti-aggregation properties against aSyn. It successfully reduced oligomeric forms of aSyn and inhibited phosphorylation in a mouse model of MSA [79]. However, a phase 1/2 study including 100 participants failed to demonstrate any significant effect [80].

Epigallocatechin gallate (EGCG) is a green tea polyphenol with a specific affinity for various beta-sheet structured proteins. It prevented aSyn aggregation and reduced neuroinflammation and oxidative stress in mouse and non-human primate models of PD [43]. However, a phase 3 trial in MSA failed to demonstrate efficacy on clinical outcomes. A small MRI sub-analysis showed lower atrophy progression in the striatum and precentral gyrus [41].

ATH434 is believed to reduce the conversion of aSyn protofibrils to fibrils through its ability to reduce the iron pool within brain structures [42]. In mouse models of MSA, it decreased aSyn burden, preserved midbrain dopamine neuron loss, and reduced motor and behavioral impairments [42, 81, 82]. ATH434 displayed favorable safety profiles and pharmacokinetics in healthy subjects [44]. A phase 2 study recruiting MSA patients is underway, with an estimated completion date in 2024 (NCT05109091). The primary endpoint is the change in the brain iron content, as MRI measured. The concept of iron chelation for treating synucleinopathies has been recently challenged. Despite promising preclinical and phase 1/2 results, deferiprone led to a deterioration of motor function in de-novo, untreated (i.e., not receiving dopamine replacement therapy) PD patients in a recent phase 3 trial [45]. This outcome was attributed to excessive iron depletion, impeding its catalytic action on tyrosine hydroxylase and causing decreased dopamine synthesis. Unlike deferiprone, ATH434 was designed to chelate iron with lower affinity [42].

Anle138b, an inhibitor of amyloid compound aggregation, has a high affinity to oligomeric forms of aSyn. It reduces the accumulation of aSyn and mitigates behavioral deficits and neurodegeneration in MSA and PD animal models [83, 84]. Phase 1 trials involving healthy subjects and PD patients showed no safety concerns and good pharmacokinetics [85, 86].

Other potential candidates for reducing aSyn aggregation are being investigated in preclinical and clinical studies. Preclinical studies reported beneficial effects of the molecular

tweezer CLR01. This nano-chaperone molecule prevents the formation of oligomeric forms of aSyn and attenuates nigral neurodegeneration [46, 47]. Similarly, belnacasan, a caspase-1 inhibitor preventing the C-terminal truncation of aSyn, decreased the formation of high molecular weight species of aSyn and mitigated inclusion formation and neurodegeneration in a transgenic mouse model of MSA [48].

Clearance Enhancer

Several candidates have been considered to enhance the clearance of aSyn through the lysosomal pathway and macroautophagy. This approach is based on preclinical studies showing that aSyn is degraded via chaperone-mediated autophagy and that aSyn aggregation impairs macroautophagy [87, 88]. Decreased nuclear levels of transcription factor EB (TFEB), a master regulator of autophagy, were found in MSA [49], and overexpression of TFEB in oligodendrocytes provided neuroprotection and decreased aSyn burden in a mouse model of MSA [49]. Given that autophagy is negatively regulated by the mammalian target of the rapamycin (mTOR) complex, mTOR inhibition with sirolimus was tested in a clinical trial. A futility analysis showed that rapamycin did not affect clinical progression or biological and neuroimaging disease markers in MSA patients [89]. This study recorded an unexpectedly high dropout rate with 22 of the 47 randomized patients who completed the required visits. Beyond early termination because of futility, one additional explanation may be a more advanced disease (i.e., patients eligible for up to 4 years after diagnosis).

Additional targets for increasing aSyn clearance are currently studied in preclinical proof-of-concept studies (Table 3) or PD/DLB clinical trials. Among these are inhibitors targeting cellular Abelson tyrosine kinase (c-Abl), which inhibits the phosphorylation of aSyn at residue 39, thereby enhancing its clearance through autophagy [50]. Several kinase inhibitors acting through the c-Abl pathway are currently being examined in clinical trials in patients with PD (NCT04691661, NCT04350177) and DLB (NCT03888222). In MSA, the compound nilotinib showed no beneficial effects in transgenic mice, but other candidates are considered [51, 52]. Additional compounds include monophosphoryl lipid A, an agonist of the Toll-like Receptor 4 that promotes microglial activation [90], the use of microRNAs of targeted genes or transcription factors that promote autophagy [91], and enzymatic degradation using the kallikrein-6 protease [92, 93].

Other Approaches

Studies have explored the potential neuroprotective properties of molecules in preventing neural loss through mechanisms that differ from the aSyn pathway. These encompass neurotrophic support, apoptosis, inflammatory processes, or mitochondrial function. Since the tested molecules may interfere with multiple pathways, the categorization below is intended to enhance understanding. The following studies are summarized in Tables 2 and 3.

For instance, riluzole was one of the first molecules tested in a large cohort of MSA patients [94]. This study achieved the most extensive recruitment of patients with MSA, with over 400 individuals. Notably, no specific outcome assessment was available during this study. Inclusions were based on operational criteria that displayed good accuracy according to a subsequent pathological validation, and the primary endpoint was overall survival. This effort highlighted the feasibility of recruiting large cohorts of patients and using survival as the primary endpoint, but the study failed its primary endpoint.

Neurotrophic Support

Selective serotonin reuptake inhibitors (SSRI) were found to have a potential effect on motor symptoms [95]. One study explored the symptomatic effect of fluoxetine but was inefficient in reducing disease progression in patients [96]. Exploratory analyses in this study showed a modest reduction in motor scores in the treated group. This ancillary result raised the question about the study's potential lack of statistical power to achieve its primary endpoint. Preclinical evidence also suggests a possible involvement of the serotonin system in MSA. Precisely, serotoninergic depletion was found in animal models of MSA, and pathological studies of patients with MSA [97, 98] and SSRI could act as neuroprotective agents in a mouse model of MSA [97, 99]

Autologous mesenchymal cell (MSC) therapy is the only intervention that significantly attenuated disease progression in MSA in a small single-center trial [100]. MSCs were administered intravenously and intra-arterially. The recruitment was limited to MSA-C patients (n=33), and the trial raised safety concerns since approximately one-third of study participants receiving intra-arterial administration experienced infraclinical ischemic stroke. Another small open-label trial (n=24) evaluated the safety and tolerability of intrathecal administration of MSCs. Patients in the high-dose group frequently complained about low back pain, in line with the thickening/enhancement of lumbar nerve roots on MRI [101]. Following the small open-label trial, a randomized phase 2 trial assessing the efficacy of intrathecal MSCs is currently recruiting patients (NCT05167721).

The monoamine oxidase inhibitor (MAOI) rasagiline was tested in a large randomized trial involving 174 patients following an indication of a neuroprotective effect in a transgenic mouse model of MSA [102]. This study failed to demonstrate any significant effect on the primary outcome, i.e., the change in total UMSARS score

or other endpoints, including neuroimaging [103]. Safinamide, another MAOI, was recently tested in an exploratory study involving 49 patients, 32 of whom received active treatment. Preliminary results showed that the proportion of adverse events was similar to that of the placebo group, but no publication of the full results is available (NCT03753763).

Other candidates are currently investigated in preclinical PD models but are also considered potential targets for MSA. KM-819, an FAF1 inhibitor, demonstrated neuroprotection in PD animal models [104]. It also exhibited favorable safety and pharmacokinetics in healthy subjects [105]. It is undergoing phase 2 trials for MSA (NCT05695378) and PD patients (NCT05670782). Phenotypic screening identified the potential of Stearoyl-CoA Desaturase (SCD) inhibition to reduce aSyn neurotoxicity [106, 107]. The SCD inhibitor YTX-7739 was well tolerated in healthy participants and PD patients, but further developments are pending [108].

Potential targets include FTY720-Mitoxy, a non-phosphorylated version of the sphingosine-1 phosphate receptor (S1PR) agonist fingolimod. It promotes neurotrophic factor release without T-cell immunosuppression and has demonstrated benefits in a mouse model, affecting aSyn pathology, neurotrophic factors, and motor functions [55, 109]. One S1PR agonist has already been tested on healthy participants (NCT04578028) and is currently recruiting MSA patients for a safety study (NCT05923866).

Epigenetic factors, like the pan-histone deacetylase inhibitor (HDACi), improved survival and motor function in an MSA mouse model [110]. Another approach involves benztropine, a muscarinic acetylcholine receptor antagonist that may enhance myelination and prevent neural cell loss [111].

Mitochondrial Dysfunction

Ubiquinol is the reduced form of coenzyme Q10 (CoQ10) essential to mitochondrial function. This approach followed the identification of rare variants and mutations in the COQ2 gene involved in CoQ10 biosynthesis and the reduction of COQ10 levels in CSF and cerebellar tissues of patients [112–115]. High doses of CoQ10 were well tolerated in healthy subjects, and patients (n=69) receiving CoQ10 demonstrated significantly slower motor progression compared to placebo (n=70) [57, 116]. Notably, the observed benefits could not be solely attributed to patients with a COQ2 mutation. Some limitations are still to be considered. Firstly, the study recruited a majority of the MSA-C subtype. Secondly, the effect size (−1.7 point difference in the UMSARS motor scale after 48 weeks of follow-up) is below what is considered clinically meaningful [117]

Modulating the Insulin/IGF1 Pathway

Growth hormone (GH) has neurotrophic effects and acts as a prohormone for IGF-1. Insulin/IGF-1 signaling contributes to nerve cell metabolism and exerts prosurvival effects. Many preclinical studies showed that IGF-1 preserves neural loss due to experimental injury, and impaired insulin/IGF1 signaling exacerbates dopamine cell loss in animal models of synucleinopathies [118]. Markers of insulin resistance correlate with aSyn burden in the brain of patients with MSA, suggesting a role in aSyn accumulation, and the antidiabetic glucagon-like peptide-1 agonist exenatide showed neuroprotective effects in transgenic MSA mice [53]. A small open-label phase 2 trial assessing the efficacy of exenatide in MSA patients is currently being conducted (NCT04431713). Similarly, knocking down GRK2, a key inhibitor of insulin signaling, showed positive effects on neural cell loss and aSyn load in a mouse model of MSA [119].

The use of recombinant GH has been assessed in a randomized placebo-controlled study involving 43 patients with MSA. Despite a trend for a positive effect on the evolution of motor symptoms, it did not reach its primary endpoint. A high dropout rate (37% of participants), leading to lower statistical power, may have contributed to this negative result [58].

Neuroinflammation and Oxidative Stress

Other strategies investigated the impact on neuroinflammation [120]. To this extent, previous trials using intravenous immunoglobulins or the antimicrobial agent minocycline failed to demonstrate a neuroprotective effect [54, 56]. The production of inflammatory oxidative species by phagocytic cells was also studied in a mouse model of MSA. When treated with a myeloperoxidase inhibitor, animals showed contrasting results on behavioral impairment and reduction of neural loss [121, 122]. In human studies, a small PET study in patients with PD showed that the myeloperoxidase inhibitor verdiperstat affects microglial activation but failed to demonstrate any clinical effect [123]. Conversely, exploratory analyses of a phase 2 study revealed a reduction in the total UMSARS progression among patients with MSA who received verdiperstat, while no significant effect was observed on microglial activation as assessed by PET imaging [59]. A larger multicentric randomized trial of 336 participants assessed the efficacy of verdiperstat on MSA patients. Notably, this study used a modified version of the UMSARS, comprising a subset of UMSARS I and II items reflecting activities of daily living, as a primary endpoint. The study failed its primary (based on clinical progression) and key secondary outcomes (NCT03952806).

Urate serum levels are negatively correlated with disease severity [124] and were associated with white matter

integrity in a diffusion-based MRI study in patients with MSA [125]. Increasing urate levels were then tested on a tolerability study using inosine 5'-monophosphate, which showed no safety concerns and may represent a potential new target for efficacy studies [126].

Other candidates are currently investigated in preclinical PD models but are also considered potential targets for MSA. KM-819, an FAF1 inhibitor, demonstrated neuroprotection in PD animal models. It also exhibited favorable safety and pharmacokinetics in healthy subjects. It is undergoing phase 2 trials in MSA (NCT05695378) and PD patients (NCT05670782). Phenotypic screening identified the potential of Stearoyl-CoA Desaturase (SCD) inhibition to reduce aSyn neurotoxicity. The SCD inhibitor YTX-7739 was presented as well tolerated in healthy participants and PD patients, but further developments are pending.

Potential targets include FTY720-Mitoxy, a non-phosphorylated version of the sphingosine-1 phosphate receptor (S1PR) agonist fingolimod. It promotes neurotrophic factor release without T-cell immunosuppression and has demonstrated benefits in a mouse model, affecting aSyn pathology, neurotrophic factors, and motor functions. One S1PR agonist has already been tested on healthy participants (NCT04578028) and is currently recruiting MSA patients for a safety study (NCT05923866).

Epigenetic factors, like the pan-histone deacetylase inhibitor (HDACi), improved survival and motor functions in an MSA mouse model. Another approach involves benztropine, a muscarinic acetylcholine receptor antagonist that may enhance myelination and prevent neural cell loss.

Conclusion

Over 30 compounds have been tested in clinical trials in MSA over the past few decades. While this illustrates a strong treatment pipeline, only two have reached their primary endpoint. Negative outcomes contrast the many preclinical studies showing positive results for compounds that later failed, highlighting the importance of better understanding underlying disease mechanisms and improving preclinical models. Finally, efforts to refine clinical measurement tools, innovative statistical methods, and developments in biomarker research will undoubtedly enhance the design of future neuroprotection trials in MSA and the likelihood of positive outcomes. Biomarkers will play an increasing role in assessing target engagement, increasing diagnostic accuracy, efficacy endpoints, and patient stratification.

Declarations

Conflict of Interest M.F. received Grants from MSA Coalition, HORIZON 2022, Honoraria to speak from BIAL, AbbVie, Orkyn, Elivie, LvL médical and consultancies from Bial, Convatec and LvL médicale.
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W.G.M. reports personal fees from Elsevier, from Biohaven, Lundbeck, Roche, Servier, Alterity, Inhibikase, Teva and Takeda, outside the submitted work; and 1. International Parkinson and movement disorder society (Treasurer and Officer) 2. MSA Coalition (Member research steering committee) 3. Clément Fayat Foundation (Board of directors).
A.P.L. reports honoraria from Biohaven, HAC Pharma and speaker fees from Alnylam, outside the submitted work.
O.R. is advising following compagnies AbbVie, Acorda, Aguettant, Alkahest, AlzProtect, Apopharma, Astrazeneca, Bial, Biogen, Britannia, Buckwang, Cerevel, Clevexel, Contera, GE Healthcare, Handltherapeutic, Ionis, Irlab, Jazz, Kyowa, LGD Nuvamid, Lundbeck, Merck, Merz, MundiPharma, Neuralight, Neuratris, Neuroderm, Novartis, ONO Pharma, Orion Pharma, Parexel, PD Neurotechnology, Pfizer, Polycaps, Prexton, Roche Therapeutics, Sanofi, Scienture, Servier, Sombiotech, Sunovion, Supernus, Synagile, Thelonius Mind, Takeda, Théranexus, Teva, Tools4patient, UCB, Vision 2 voice, Zambon.
C.P.L., D.B., F.S., P.O.F., and T.S. have nothing to disclose.

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- • Of importance
- •• Of major importance

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