Editorial Commentary

Epigallocatechin gallate in multiple system atrophy (PROMESA)

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Multiple system atrophy (MSA) is a rapidly progressing, fatal neurodegenerative disease of unclear etiology, clinically characterized by parkinsonism, cerebellar impairment, autonomous and motor dysfunctions in any combination due to degeneration of striatonigral, olivopontocerebellar and autonomous nervous systems (1,2). Pathological hallmarks are fibrillary α-synuclein (αSyn)-rich inclusions in oligodendroglia (glial cytoplasmic inclusions/GCIs) (3) that also rarely involve astrocytes and neurons (4). The pathogenic cascade leading to αSyn aggregation and multisystem neurodegeneration in this oligodendroglioneuronal synucleinopathy are unclear, but convincing evidence suggests a "prion-like" spreading of misfolded αSyn strains as key event of the pathogenesis of MSA (5,6). However, the prion hypothesis of human synucleinopathies and the question whether αSyn is a prion or prion-like are a matter of continuing discussion (7-9). So far no causative or disease-modifying treatments are available and symptomatic therapies are limited (10). Numerous randomised, placebo-controlled trials of putative disease-modifying agents—including riluzole, minocyline, lithium, rifampicin, fluoxetine, rasagilin, neuroprotective MSC, EGCG, intravenous immunoglobulins (IVIg) and others—most of them efficient in cellular or animal models of MSA, in human patients showed no clinical effects (7,10-12). Targeting the "prion-like" cell-to-cell propagation of αSyn, immunotherapy showed decreased accumulation of αSyn, and reduced demyelination in models of MSA (13,14), while a combination of a single-chain antibody and anti-inflammatory compounds (lenalidomide) ameliorated αSyn accumulation, gliosis, and behavioral deficits in MBP-αSyn transgenic mice (15). A phase I study using specific active immunotherapy against αSyn, in healthy volunteers revealed favorable safety, tolerability and pharmacokinetic parameter (16). Passive immunotherapy clinical trials with AFFITOPE vaccine have been performed and other clinical trials with passive immunotherap are ongoing (7). Application of autologous mesenchymal stem cells (MSCs) showed immunomodulation and neuroprotective effects in trangenic mouse models of MSA (17), and intrathecal application of human umbilical cord blood-mononuclear cells (hUCB-MNC) in a small number of patients with MSA was reported to have shown clinical effects without serious complications (18), but neither clinical details nor validation of these Chinese trials are available. A clinical trial using intra-arterial and intravenous injection of MSCs was reported to delay disease progression in patients with MSA-C (19). Another phase I clinical trial of intrathecal administration of autologous MSCs in MSA patients was conducted by the Mayo Clinic (20).

New strategis targeting αSyn aggregation are in progress, based on trial by the MSA Coalition (1). Inhibition of αSyn aggregation is one of rational therapeutic interventions to target a key pathophysiological process (21,22). The polyphenol epigallocatechin gallate, a compound approved as dietary supplement but possibly hepatotoxic at higher doses (23), inhibits αSyn aggregation and reduces associated toxicity in cultures and animal model of synucleinopathies (24). A recent randomised, double-blind clinical trial at 12 German centers in 92 participants (47 assigned to epigallocatechine gallate, given orally as capsules: 400 mg/day for 4 weeks increasing to 3 doses/day for 40 weeks, and 45 to placebo) was

performed by the PROMESA study group to investigate the safety and efficency of the compound as a first-in-class αSyn oligomer modulator in patients with possible or probable MSA (12). Primary outcome was the change from baseline to week 52 in motor examination scores on UMSAR (25). The study showed no difference in the mean clinical changes from baseline to week 52, and, thus, was not associated with clinically relevant disease modification in patients with MSA compared to placebo. Furthermore, the drug had no effect on the secondary clinical outcome measures (i.e., clinical global impression or UMSARS total scores). The drug was overall well tolerated but was associated with hepatotoxic effects in some patients, and therefore doses of more than 1.200 mg should be avoided. However, results of an exploratory MRI sub-study in 17 patients and 15 controls suggested that epigallocatechin gallate can slightly reduce striatal volume loss, which might suggest its neuroprotective effects, although other explanations cannot be excluded, e.g., modulation of inflammatory processes or increasing water content (12). The limitations of this PROMESA trial, discussed by the authors, were the comparatively small numbers of patients in some of the 12 study centers, the comparatively large number of drop-outs (28%) and the limited observation time (12). In addition, one should take into account that the acurracy of the clinical diagnosis of MSA is still unsatisfactory with a positive predictive value even in later stages ranging from 60% to 90% (7). Similarly, most of clinical trials failed to show positive results, probably because of small numbers of enrolled patients and the inevitable involvement of non-MSA patients. Despite these caveats, exploratory evidence of the PROMESA trial supports the assumption that αSyn oligomer formation might be a valid target for treatment of MSA for future trials, these should include larger numbers of patients, longer observation periods, and larger numbers of partizipating centers in order to enable the urgently needed detection of disease-modifying treatment strategies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Krismer F, Wenning GK. Multiple system atrophy: insights into a rare and debilitating movement disorder. Nat Rev Neurol 2017;13:232-43.
2. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670-6.
3. Trojanowski JQ, Revesz T. Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy. Neuropathol Appl Neurobiol 2007;33:615-20.
4. Cykowski MD, Coon EA, Powell SZ, et al. Expanding the spectrum of neuronal pathology in multiple system atrophy. Brain 2015;138:2293-309.
5. Goedert M, Masuda-Suzukake M, Falcon B. Like prions: the propagation of aggregated tau and alpha-synuclein in neurodegeneration. Brain 2017;140:266-78.
6. Jellinger KA. Multiple system atrophy: an oligodendroglioneural synucleinopathy. J Alzheimers Dis 2018;62:1141-79.
7. Koga S, Dickson DW. Recent advances in neuropathology, biomarkers and therapeutic approach of multiple system atrophy. J Neurol Neurosurg Psychiatry 2018;89:175-84.
8. Steiner JA, Quansah E, Brundin P. The concept of alpha-synuclein as a prion-like protein: ten years after. Cell Tissue Res 2018;373:161-73.
9. Woerman AL, Oehler A, Kazmi SA, et al. Multiple system atrophy prions retain strain specificity after serial propagation in two different Tg(SNCA*A53T) mouse lines. Acta Neuropathol 2019;137:437-54.
10. Maaß S, Levin J, Hoglinger G. Current treatment of multiple system atrophy. Curr Treat Options Neurol 2016;18:51.
11. Meissner WG, Fernagut PO, Dehay B, et al. Multiple system atrophy: recent developments and future perspectives. Mov Disord 2019;34:1629-42.
12. Levin J, Maass S, Schuberth M, et al. Safety and efficacy of epigallocatechin gallate in multiple system atrophy (PROMESA): a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2019;18:724-35.
13. Schneeberger A, Tierney L, Mandler M. Active immunization therapies for Parkinson's disease and multiple system atrophy. Mov Disord 2016;31:214-24.

14. Mandler M, Valera E, Rockenstein E, et al. Active immunization against alpha-synuclein ameliorates the degenerative pathology and prevents demyelination in a model of multiple system atrophy. Mol Neurodegener 2015;10:10.
15. Valera E, Spencer B, Fields JA, et al. Combination of alpha-synuclein immunotherapy with anti-inflammatory treatment in a transgenic mouse model of multiple system atrophy. Acta Neuropathol Commun 2017;5:2.
16. Meissner W, Pavy-Le Traon A, Foubert-Samier A, et al. Specific active immunotherapy (SAIT) against alpha-synuclein with AFFITOPE® PD01A and PD03A: Results from the AFF009 phase I trial. Mov Disord 2018;33:abstr 7.
17. Na Kim H, Yeol Kim D, Hee Oh S, et al. Feasibility and efficacy of intra-arterial administration of mesenchymal stem cells in an animal model of double toxin-induced multiple system atrophy. Stem Cells Transl Med 2017;6:1424-33.
18. Yu H, Yuan X, Liu L, et al. Treatment of multiple system atrophy - the past, present and future. Am J Clin Exp Immunol 2018;7:88-94.
19. Lee PH, Lee JE, Kim HS, et al. A randomized trial of mesenchymal stem cells in multiple system atrophy. Ann Neurol 2012;72:32-40.
20. Singer W, Dietz AB, Zeller AD, et al. Intrathecal administration of autologous mesenchymal stem cells in multiple system atrophy. Neurology 2019;93:e77-e87.
21. Dehay B, Bourdenx M, Gorry P, et al. Targeting alpha-synuclein for treatment of Parkinson's disease: mechanistic and therapeutic considerations. Lancet Neurol 2015;14:855-66.
22. Heras-Garvin A, Weckbecker D, Ryazanov S, et al. Anle138b modulates alpha-synuclein oligomerization and prevents motor decline and neurodegeneration in a mouse model of multiple system atrophy. Mov Disord 2019;34:255-63.
23. Dekant W, Fujii K, Shibata E, et al. Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements. Toxicol Lett 2017;277:104-8.
24. Xu Q, Langley M, Kanthasamy AG, et al. Epigallocatechin gallate has a neurorescue effect in a mouse model of Parkinson disease. J Nutr 2017;147:1926-31.
25. Wenning GK, Tison F, Seppi K, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 2004;19:1391-402.

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