Title

GLP-1 in Multiple Sclerosis: preclinical evidence, clinical prospects and future directions

Author

Dmitry Satanovsky, MD, Neurologist

Affiliation

Private Neurology Practice, Ukraine

ORCID

0009-0008-7530-9404

Correspondence

E-mail: dr.dmitrysat@gmail.com

Abstract

Background: Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation, demyelination and neurodegeneration. Despite the availability of disease modifying drugs, the progressive disability remains a major unmet need.

Objective: Review preclinical and emerging clinical data on the potential use of GLP-1 receptor agonists in multiple sclerosis (MS) and neuroinflammation, remyelination and MS outcomes in a meta-meta-data search in the PubMed and Scopus (2018-25).

Results: In experimental autoimmune encephalomyelitis, semaglutide, liraglutide and dulaglutide resulted in a reduction in inflammation, improvement in neurological scores and an increase in remyelination. Observation data in patients with diabetes or obesity treated with GLP-1R showed no worsening of the disease course and pharmacovigilance analyses suggested a potential protective signal. GLP-1RAs have also been shown to be neuroprotective in Alzheimer's disease and Parkinson's disease and may support their role in neurodegeneration. Ongoing clinical studies evaluate brain atrophy, serum neurofilament light and cognition. While the early data are encouraging, controlled clinical trials are needed to determine the efficacy and safety of the product.

Keywords

GLP-1 receptor agonists; multiple sclerosis; neuroinflammation; remyelination; liraglutide; semaglutide

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS), which includes inflammatory demyelination and axonal loss and neurodegeneration. Although disease modifying drugs (DMTs) are currently available to reduce relapse and the MRI activity of relapsing disease, many patients develop irreversible disability. There is a need for drugs that can provide neuroprotection and remyelination in addition to immunomodulation and several candidates have emerged, including peptide-1 receptor agonists (GLP-1RA).

From metabolic disorders to neuroprotection

GLP-1RAs such as semaglutide, liraglutide, dulaglutide are developed to prevent the onset of diabetes and to lose weight. Besides metabolic effects, several CNS-related mechanisms have been described: inhibition of proinflammatory cytokines (TNF-alpha, IL-1b, IL-6); inhibition of microglial and astrocytic activation; inhibition of neuronal apoptotic signaling; stimulation of PI3K and GSK-3b; and reduction of oxidative stress [1-4,12,14]. The pleiotropic properties of GLP-1R make them a potential target for neuroinflammatory disorders, such as Multiple Sclerosis.

Preclinical evidence

The most used animal model for MS is experimental autoimmune encephalomyelitis (EAE). In EAE, semaglutide reduced clinical severity, axonal protection and myelin preservation [1]; liraglutide reduced inflammatory infiltrates and reduced pro-inflammatory cytokines [2]; dulaglutide increased remyelination and axonal injury [3]. NLY01, a GLP-1A investigational product, has been shown to provide neuroprotection in EAE and cuprizone demyelination and to support glia-mediated neuroinflammation and myelin repair [4]. Systematic evaluation of preclinical data consistently indicates that GLP-1ARA has anti-inflammatory and neuroprotective profiles in demyelinating models.

Clinical observations

To date, no randomized, controlled trial has been completed with GLP-1RA in patients with multiple sclerosis. Observation series in patients with diabetes or obesity have shown no deterioration in the activity of the MS during exposure to GLP-1RIA [7]. Pharmacovigilance analyses using FAERS have reported an inverse association between the use of semaglutide and the number of Member States reporting, although these signals are tentative and prone to bias [5,6]. An abstract presented at AANJ Neurology suggested a slower progression to disability in GLP-1RAs, but the results are still preliminary pending peer review [8]. The comprehensive

pharmacovigilance review did not identify any major neurological safety concerns specific to GLP-1RA and highlighted the lack of MS-related results [9].

Evidence from other neurodegenerative diseases

GLP-1RA have been evaluated in Alzheimer's disease (AD) and Parkinson's disease (PD). In AD models, these agents improved cognition, reduced amyloid pathology and tau, and mitigated neuroinflammation; meta-analytic syntheses support benefits mediated by mitochondrial and synaptic pathways [13,14]. In PD models, liraglutide and exenatide reduced dopaminergic neuron loss and neuroinflammation; clinical meta-analyses indicate acceptable safety and potential motor improvement [15–17]. Cross-disease evidence strengthens the biological plausibility of GLP-1RA as a neuroprotective agent.

Ongoing clinical trials

In 2025, a single-center study was started at the University of Comenius (Bratislava) to evaluate semaglutide (oral) and dulaglutide in MS with highly active relapsing-remitting lesions, as well as in MRI, serum neurofilament light chain and cognitive measures; the study is scheduled to be completed in 2026 [10,11]. The results will clarify the feasibility and magnitude of any effects related to the disease.

Limitations and safety considerations

GLP-1RAs are approved for type 2 diabetes and obesity; they are not approved for use in multiple sclerosis. There is no evidence of a reduction in recidivism or of a slowing in the rate of final disability. Typical side effects are gastrointestinal symptoms and weight loss, which may be unwanted in patients who are underweight. Long-term neurological safety in multiple sclerosis has not been established and the cost of and chronic use of the product may restrict access [5,9]. Strong randomized studies with imaging and liquid biomarkers are required.

Conclusion

GLP-1 receptor agonists represent a reliable and mechanistically supported route of additional neuroprotection and potential remyelination in multiple sclerosis, with robust preclinical data

and preliminary clinical observations that are reassuring but not conclusive. Until the outcome of randomized trials is available, GLP-1RA should be considered experimental in the Member States.

Declarations

Funding: None.

Conflicts of interest: The author declares no conflicts of interest.

Ethics approval: Not applicable; this is a narrative review of published literature.

Consent to participate/publish: Not applicable.

Data availability: All data cited are from published sources.

Acknowledgments: None.

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