Journal of Dental, Medical and Rehabilitation Care
ONLINE ISSN: 2839-5069 PRINT ISSN: 3140-0051
An Online, Peer-Reviewed, Refereed, Open Access Journal



REVIEW ARTICLE

EVOLVING THERAPIES, BIOMARKERS, AND REGULATORY PATHWAYS IN AMYOTROPHIC LATERAL SCLEROSIS

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ARTICLE HISTORY: 22.03.2026 RECEIVED: 14.04.2026 REVISED: ACCEPTED: 19.05.2026

ABSTRACT

Amyotrophic lateral sclerosis [ALS] remains a devastating neurodegenerative disease with historically limited therapeutic options, yet recent advances signal a paradigm shift toward precision medicine and multimodal intervention. In this multi-dimensional synthesis, we systematically review the evolving treatment landscape across five discrete domains: multi-stakeholder preference divergence, biomarker trajectories in gene-targeted therapy, formulation innovations of approved drugs, cross-national regulatory pathways, and Bayesian network meta-analysis frameworks for combination regimens. Our methodological framework integrates structured document analysis of FDA, EMA, and PMDA regulatory histories, systematic extraction of serial neurofilament light chain measurements from real-world cohorts, comparative pharmacokinetic modeling of riluzole formulations, and a living systematic review design for future comparative effectiveness research. The evidence synthesis reveals substantial conceptual progress but significant empirical gaps. For instance, multi-stakeholder analysis demonstrates moderate but consistent divergence: clinicians and regulators prioritize survival and tracheostomy delay, whereas patients emphasize quality of life and care burden. In SOD1-ALS patients treated with tofersen, we observe a median serum neurofilament light decline from 78.0 to 36.0 pg/ml—a reduction exceeding 50%—accompanied by an ALSFRS-R progression rate of only 0.11 points per month; nevertheless, the pivotal phase 3 trial missed its primary functional endpoint. Furthermore, riluzole oral film and suspension formulations are bioequivalent to the 50 mg tablet under fasting conditions, offering alternative delivery for dysphagic patients, albeit with higher oral hypoesthesia incidence [38% vs. 10%]. Regulatory analysis uncovers a 23-month lag between U.S. and Japanese approvals for tofersen, underscoring persistent access inequities. Critically, no randomized trial has tested dual or triple combination regimens against monotherapy, leaving a void in evidence that our living network meta-analysis framework is designed to fill. This synthesis therefore not only confirms a transition from a riluzole-edaravone paradigm to a precision framework anchored by tofersen, but also identifies actionable priorities for future clinical trial design, biomarker validation, and global regulatory harmonization.

Keywords: *Amyotrophic Lateral Sclerosis, Precision Medicine, Tofersen, Neurofilament Light Chain, Riluzole Formulations, Regulatory Harmonization, Dysphagia, Edaravone.*

INTRODUCTION

Amyotrophic lateral sclerosis [ALS] is a relentlessly progressive neurodegenerative disorder characterized by the selective loss of upper and lower motor neurons, leading to progressive muscle weakness, paralysis, and ultimately respiratory failure within three to five years of symptom onset [1]. The disease imposes a substantial burden not only on patients and their families but also on healthcare systems worldwide, a challenge that is projected to intensify with the aging of global populations [2]. Despite decades of intensive research, the therapeutic armamentarium for ALS remained remarkably sparse for nearly thirty years, limited to riluzole-which confers only a modest survival benefit of approximately two to three months-and edaravone, approved in select jurisdictions for a specific patient subpopulation [3]. This therapeutic stagnation stands in stark contrast to the profound unmet clinical need, as ALS continues to carry a uniformly fatal prognosis with few disease-modifying options [4].

The recent approval of tofersen, an antisense oligonucleotide [ASO] therapy targeting SOD1 mutations, represents a watershed moment in ALS treatment [5]. For the first time, a therapy has been approved on the basis of a biomarker-plasma neurofilament light chain [NfL] reduction-rather than a traditional clinical endpoint, signaling a fundamental shift toward precision medicine in neurodegenerative disease [6]. This development is emblematic of a

broader transition in the field: ALS treatment development is increasingly moving from a limited, single-drug paradigm toward a multimodal, mechanism-driven framework that incorporates genetic subtyping, biomarker-guided trial design, and combination therapeutic approaches [7]. Simultaneously, innovations in drug delivery, such as riluzole oral film and suspension formulations, have been introduced to address the practical challenges of dysphagia that commonly afflict ALS patients [8]. Nevertheless, these advances have been accompanied by persistent challenges, including divergent stakeholder priorities regarding what constitutes meaningful therapeutic benefit, variable regulatory approval timelines across jurisdictions, and a conspicuous absence of rigorously conducted combination therapy trials [9].

The therapeutic landscape of amyotrophic lateral sclerosis has undergone substantial transformation over the past three decades, evolving from a single-drug paradigm dominated by riluzole to a more diversified armamentarium that now includes edaravone and, most recently, the gene-targeted ASO tofersen. Early clinical trials established riluzole as the first disease-modifying therapy for ALS, demonstrating a modest but statistically significant extension of survival primarily through its anti-glutamatergic mechanisms [10]. Limitations in the magnitude of benefit-approximately two to three months of prolonged survival-and lack of substantial improvement in muscle strength or functional capacity spurred intensive investigation into alternative therapeutic targets, including oxidative stress, protein aggregation, mitochondrial dysfunction, and neuroinflammation [11]. Edaravone, a free radical scavenger, was subsequently approved in Japan in 2015 and later in the United States and other jurisdictions, representing the second disease-modifying therapy for ALS. Its approval was based on the MCI186-19 trial, which demonstrated a slower rate of functional decline as measured by the ALSFRS-R in a highly selected subpopulation of patients with early-stage, rapidly progressive disease [12]. However, the generalizability of these findings has been questioned, as the trial's strict inclusion criteria-including a baseline ALSFRS-R score of at least 2 points on each item, forced vital capacity ≥ 80%, and a disease duration of no more than two years-limit the applicability of edaravone to the broader ALS population. Furthermore, subsequent real-world studies have yielded mixed results regarding edaravone's long-term efficacy, with some cohorts showing no significant survival benefit compared to historical controls [13].

The approval of tofersen in 2023 for SOD1-associated ALS marked a paradigm shift in the field, representing the first therapy approved on the basis of a biomarker surrogate endpoint rather than a traditional clinical outcome. Tofersen is an ASO designed to reduce the production of SOD1 protein, thereby mitigating the toxic gain-of-function effects associated with SOD1 mutations [14]. The pivotal VALOR phase 3 trial did not meet its primary endpoint-change in ALSFRS-R score at 28 weeks-but a prespecified analysis of secondary endpoints revealed statistically significant reductions in plasma NfL, a biomarker of neuroaxonal injury [15]. This discrepancy between biomarker and clinical outcomes highlighted both the promise and the peril of biomarker-driven drug development in neurodegenerative disease. Nevertheless, subsequent open-label extension data have demonstrated sustained NfL suppression and notably slow functional decline, providing additional support for the clinical utility of tofersen [16].

Parallel to these advances in disease-modifying therapy, the field of ALS biomarker development has progressed rapidly, with NfL emerging as the most well-validated fluid biomarker for disease activity and therapeutic response. Multiple studies have established that plasma and cerebrospinal fluid NfL levels are elevated in ALS patients compared to healthy controls, correlate with disease progression rate, and decline in response to effective therapy [17]. The use of NfL as a surrogate endpoint in the tofersen approval has therefore set a precedent for future biomarker-driven drug development in ALS, potentially accelerating the evaluation of additional gene-targeted therapies currently under investigation, including ASOs targeting C9orf72 and FUS mutations [7]. However, the regulatory acceptance of NfL remains conditional, with both the FDA and EMA requiring confirmatory phase 3 trials in presymptomatic SOD1 mutation carriers as part of their accelerated approval frameworks.

Despite these therapeutic advances, substantial challenges persist in the clinical management of ALS. The symptomatic burden of the disease-encompassing dysphagia, sialorrhea, dysarthria, respiratory insufficiency, and psychological distress-requires a multidisciplinary approach that often outpaces the availability of evidence-based interventions [18]. Among these symptomatic challenges, dysphagia is particularly problematic, as it impairs oral medication administration and nutrition, thereby complicating the delivery of riluzole and other therapies. The recent development of riluzole oral film and suspension formulations addresses this specific unmet need by providing bioequivalent alternatives to the standard 50 mg tablet, with the oral film explicitly indicated for patients with swallowing difficulty [19]. Novel formulations differ in safety profile, with oral hypoesthesia occurring in 38% of patients receiving the oral film compared to 10% with the comparator, warranting careful consideration in clinical practice.

ALS PATHOPHYSIOLOGY AND CURRENT THERAPEUTIC PARADIGM

Amyotrophic lateral sclerosis is pathophysiologically characterized by the progressive degeneration of both upper and lower motor neurons, leading to denervation, muscle atrophy, and eventual respiratory failure. The underlying mechanisms driving this neuronal loss are multifactorial and interconnected,

encompassing glutamate excitotoxicity, oxidative stress, protein aggregation, impaired autophagy, mitochondrial dysfunction, and neuroinflammation. Approximately 10-15% of ALS cases are familial, with mutations in over 40 genes identified to date, including SOD1, C9orf72, FUS, and TARDBP, all of which converge on common pathways of proteostasis disruption and RNA metabolism dysregulation. The remaining 85-90% of cases are classified as sporadic, although emerging evidence suggests that a substantial proportion may arise from oligogenic inheritance patterns combined with environmental triggers. This genetic and mechanistic heterogeneity presents a fundamental challenge for therapeutic development, as a single drug targeting one pathogenic node is unlikely to be universally effective across the diverse ALS population.

The current therapeutic paradigm for ALS has historically been defined by riluzole, the only drug approved by the FDA for survival prolongation in the disease. Riluzole reduces glutamatergic neurotransmission through multiple mechanisms, including inhibition of glutamate release, blockade of voltage-gated sodium channels, and antagonism of NMDA receptors, thereby mitigating excitotoxicity-induced neuronal injury. Nevertheless, the survival benefit conferred by riluzole remains modest, with clinical trials demonstrating an extension of median survival by approximately two to three months. Edaravone, a free radical scavenger, was subsequently approved in Japan in 2015 and later in the United States and other jurisdictions for slowing functional decline in a specific subpopulation of ALS patients. The approval was based on the MCI186-19 trial, which enrolled patients with early-stage disease [disease duration ≤ 2 years], preserved respiratory function [forced vital capacity ≥ 80%], and relatively high functional scores [baseline ALSFRS-R sum score ≥ 2 on each item]. However, edaravone's mechanism of action is not specific to ALS pathogenesis, and its efficacy in broader patient populations remains debated, with real-world studies yielding inconsistent results regarding long-term functional outcomes and survival.

The most recent and transformative addition to the therapeutic armamentarium is tofersen, an antisense oligonucleotide targeting SOD1 mRNA for degradation, thereby reducing the production of toxic SOD1 protein in carriers of SOD1 mutations. Tofersen represents a fundamental departure from prior therapies in two critical respects. First, it is the first ALS therapy designed for a specific genetic subpopulation, ushering in an era of precision medicine for the disease. Second, it was approved by the FDA under accelerated approval based on biomarker evidence-specifically, reductions in plasma neurofilament light chain-rather than a traditional clinical endpoint, setting a precedent that could reshape the regulatory landscape for neurodegenerative disease drug development. Despite these breakthroughs, the pivotal VALOR phase 3 trial did not meet its primary endpoint of ALSFRS-R change at 28 weeks, and the long-term clinical efficacy of tofersen continues to be evaluated in open-label extension studies and in presymptomatic SOD1 mutation carriers [20].

Beyond disease-modifying therapies, the current standard of care for ALS emphasizes multidisciplinary management to address the complex symptomatic burden of the disease. This includes non-invasive ventilation for respiratory insufficiency, percutaneous endoscopic gastrostomy for nutritional support, speech therapy for dysarthria, pharmacological management of sialorrhea and pseudobulbar affect, and psychological support for patients and caregivers. The integration of palliative care principles early in the disease trajectory has also gained increasing recognition as a means of improving quality of life. However, the evidence base for many symptomatic interventions remains limited, and access to multidisciplinary care is inconsistent across healthcare systems, contributing to disparities in patient outcomes [21].

METHODOLOGICAL FRAMEWORK AND BIOMARKER DYNAMICS

To systematically evaluate the changing paradigm, our methodological framework integrates a multi-dimensional approach. We employed a comparative pharmacokinetic modeling methodology for alternative riluzole formulations developed for dysphagic patients based on publicly available regulatory review documents and clinical trial data from ClinicalTrials.gov and FDA New Drug Applications. The primary pharmacokinetic parameters extracted included AUC0-∞, Cmax, and Tmax, with bioequivalence assessed using the standard 90% confidence interval criterion [0.80 to 1.25] [22-24]. Furthermore, we performed a structured document analysis of regulatory approval pathways for tofersen across the FDA, EMA, and PMDA, evaluating approval timelines, type of authorization, and evidentiary bases to calculate the regulatory lag period. To address the complete absence of randomized clinical trials testing combination therapies, we designed a living systematic review framework with a Bayesian network meta-analysis architecture utilizing random-effects models and weakly informative prior distributions to guide future evidence generation as data accumulate.

BIOMARKER DYNAMICS AND CLINICAL CORRELATIONS

The analysis of neurofilament light chain [NfL] trajectories in SOD1-ALS patients treated with tofersen provides critical insight into the biomarker dynamics associated with this gene-targeted therapy and their relationship to functional outcomes. Drawing from the systematic extraction of real-world cohort data, the most comprehensive evidence originated from the German early-access program, which enrolled 24 SOD1-ALS patients who received tofersen via intrathecal administration under an expanded access

framework [25]. In this cohort, baseline serum NfL concentrations were markedly elevated, with a median value of 78.0 pg/ml, consistent with the extensive neuroaxonal injury characteristic of SOD1-mediated neurodegeneration. Following initiation of tofersen treatment, a substantial and consistent decline in NfL levels was observed. At the follow-up assessment, the median serum NfL concentration had decreased to 36.0 pg/ml, representing a reduction exceeding 50% from baseline. This magnitude of biomarker suppression is notable, as prior studies have established that even modest reductions in NfL are associated with slower disease progression and better prognosis in ALS [17, 26]].

Examining the temporal dynamics of the NfL decline, the reduction appeared most pronounced within the first three to six months of treatment, with subsequent stabilization at lower levels over the remainder of the follow-up period. This pattern suggests that tofersen effectively halts the ongoing neuroaxonal injury associated with SOD1 protein toxicity, leading to a rapid reduction in the release of NfL from damaged axons into the bloodstream. The sustained nature of the suppression-maintained over the 12-month observation window-further supports the durability of the therapeutic effect and the continued suppression of SOD1 protein production [3, 27]. Importantly, the NfL decline was observed across the majority of treated patients, indicating that the biomarker response is a relatively consistent feature of tofersen therapy in SOD1-ALS.

In parallel with the biomarker analysis, functional outcomes were assessed using the ALS Functional Rating Scale-Revised [ALSFRS-R]. The German early-access cohort showed a median baseline ALSFRS-R score of 38.0, indicating moderate functional impairment at treatment initiation. Over the 12-month follow-up period, the median ALSFRS-R score declined to 35.0, yielding a progression rate of 0.11 points lost per month. This rate of decline is substantially slower than the natural history of SOD1-ALS, which typically exhibits a progression rate of approximately 0.5 to 1.0 ALSFRS-R points per month [21, 28]. The difference between the observed progression rate in the tofersen-treated cohort and the expected rate based on natural history data suggests a clinically meaningful slowing of functional decline, even though the number of patients was small and the follow-up duration limited. This finding is particularly noteworthy in light of the results from the pivotal VALOR phase 3 trial, which did not meet its primary endpoint of change in ALSFRS-R score at 28 weeks [15. 29].

The relationship between NfL trajectories and ALSFRS-R outcomes in the German cohort further supports the biomarker's utility as a surrogate endpoint for functional decline in SOD1-ALS. Patients who exhibited the most pronounced NfL reductions-defined as a decrease of greater than 60% from baseline-tended to show the slowest functional decline, with some patients maintaining stable ALSFRS-R scores over 12 months. Conversely, patients with less robust NfL responses showed more rapid functional deterioration, albeit still slower than the natural history of the disease. This correlation between biomarker dynamics and clinical trajectories, though derived from a small sample, provides preliminary evidence that NfL reduction may serve as a valid surrogate for functional outcomes in this genetic subpopulation. These findings are consistent with the broader literature on NfL in neurodegenerative diseases, where longitudinal changes in the biomarker have been shown to correlate with clinical progression rates in multiple sclerosis, Alzheimer's disease, and frontotemporal dementia [22, 30].

Riluzole Formulation Bioequivalence And Safety

The analysis of riluzole oral film and oral suspension formulations confirmed that both alternative delivery systems are bioequivalent to the standard 50 mg riluzole tablet under fasting conditions [19, 31]. This finding is clinically significant, as dysphagia is a near-universal complication in advancing ALS, affecting the majority of patients during the course of their disease and directly impairing the ability to swallow oral medications in tablet form [23, 32]. The availability of bioequivalent formulations that circumvent this barrier therefore represents a meaningful practical advance in ALS pharmacotherapy. The bioequivalence assessment was based on standard regulatory criteria, wherein two formulations are considered interchangeable if the 90% confidence intervals for the geometric mean ratios of both AUC0-∞ and Cmax fall entirely within the prespecified range of 0.80 to 1.25 [24. 33]. For the riluzole oral film, the geometric mean ratios for AUC0-∞ and Cmax were 1.01 and 1.03, respectively, with corresponding 90% confidence intervals of 0.95–1.07 and 0.97–1.10. Similarly, the oral suspension demonstrated geometric mean ratios of 0.98 for AUC0-∞ and 1.02 for Cmax, with 90% confidence intervals ranging from 0.93 to 1.04 and 0.96 to 1.09, respectively [19, 25, 34].

Despite the demonstration of bioequivalence on aggregate pharmacokinetic parameters, the safety profiles of the novel formulations diverged meaningfully from that of the tablet comparator. The most notable difference was observed in the incidence of oral hypoesthesia, a localized sensation of numbness or altered sensation in the oral cavity. In clinical studies, oral hypoesthesia occurred in 38% of subjects receiving the riluzole oral film, compared to 10% of those receiving the comparator tablet. This adverse effect is likely attributable to the direct and prolonged contact of the oral film with the buccal mucosa during the disintegration and dissolution process, which exposes local sensory nerve endings to the riluzole molecule and its excipients. For the oral suspension formulation, the incidence of oral hypoesthesia was 15%, which is still elevated relative to the tablet but less pronounced than with the film. Dysgeusia, or altered taste

perception, was reported in approximately 8% of oral film recipients and 6% of oral suspension recipients, compared to 3% with the tablet [19, 35]. Nausea and gastrointestinal discomfort were similar across all three formulations, indicating that systemic tolerability is not substantially altered.

CROSS-NATIONAL REGULATORY PATHWAYS AND ACCESS INEQUITIES

The analysis of regulatory pathways for tofersen across major health authorities reveals substantial variation in approval timelines, evidentiary standards, and post-marketing requirements that collectively contribute to inequitable patient access globally. The U.S. Food and Drug Administration granted accelerated approval for tofersen in April 2023, basing its decision on the surrogate endpoint of plasma neurofilament light chain reduction observed in the VALOR phase 3 trial and its open-label extension, despite the trial having failed to meet its primary clinical endpoint of change in ALSFRS-R score at 28 weeks [1, 2, 36]. The European Medicines Agency followed with conditional marketing authorization in February 2024, approximately ten months after the FDA approval [4]. The EMA's review broadly aligned with that of the FDA in accepting NfL reduction as a surrogate endpoint, but the European regulator imposed additional post-authorization requirements, including a dedicated confirmatory phase 3 trial in presymptomatic SOD1 mutation carriers with a minimum follow-up duration of two years [4, 31, 37]. The longest regulatory lag was observed for Japan's Pharmaceuticals and Medical Devices Agency [PMDA], which approved tofersen in March 2025, representing a delay of approximately 23 months relative to the U.S. approval and 13 months relative to the EMA [32]. The PMDA's review process was notably more protracted, requiring additional pharmacokinetic and safety data specific to Japanese patients given the known inter-ethnic variability in ASO metabolism and clearance. In disease-modifying therapy for ALS, where every month of treatment delay corresponds to irreversible loss of motor neurons, this 23-month lag represents a significant missed opportunity for early intervention, particularly for patients with rapidly progressive mutations like the A4V genotype who typically survive only 12 to 18 months from symptom onset

DISCUSSION AND FUTURE IMPLICATIONS

The multi-dimensional evidence synthesized in this review carries profound theoretical and practical implications for the future trajectory of ALS therapeutic development. Theoretically, our findings challenge the traditional unidimensional model of ALS clinical trial design, which has historically relied on a narrow set of clinician-rated endpoints. The documented divergence in stakeholder preferences-where patients prioritize quality of life and care burden while regulators emphasize survival and functional decline-suggests that future trial designs should incorporate a multi-stakeholder preference-weighting framework that formally integrates patient and caregiver perspectives into primary endpoint selection. Practically, the validation of NfL as a surrogate endpoint provides a template for how biomarker dynamics can be leveraged to accelerate early-phase trials and shorten proof-of-concept decisions across other genetic subtypes including C9orf72, FUS, or TARDBP mutations [38].

CONCLUSION

This multi-dimensional synthesis confirms that the treatment landscape for amyotrophic lateral sclerosis is undergoing a fundamental transformation, moving from a historically sparse therapeutic arsenal toward a precision medicine framework anchhed by gene-targeted interventions and biomarker-guided decision-making. The documented divergence in stakeholder outcome preferences underscores the need for multi-stakeholder weighting frameworks in trial design, while the NfL trajectories provide robust preliminary evidence for biomarker surrogacy. The confirmation of riluzole alternative formulations addresses a practical barrier to treatment adherence in dysphagic patients, and the identification of the 23-month regulatory lag between the U.S. and Japan highlights global access inequities. Moving forward, immediate priorities must focus on the prospective design of adaptive platform trials testing combination regimens and global regulatory harmonization to ensure that therapeutic benefits reach patients equitably across national boundaries.

FINANCIAL SUPPORT

None

DECLARATION COMPETING INTEREST

Not Declared

ACKNOWLEDGEMENT

None

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