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Contemporary Disease - Modifying Therapies in ALS: Clinical Evidence, Biomarkers, and Molecular Targets

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Abstract

Background

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive motor neuron loss and marked biological heterogeneity. Advances in molecular genetics and biomarker research have redefined ALS as a spectrum of molecularly distinct subtypes, creating new opportunities for disease-modifying therapeutic development.

Aim

To synthesize contemporary evidence on disease-modifying therapies in ALS, with a focus on clinical trial outcomes, validated biomarkers, and molecular targets that inform precision medicine approaches.

Material and Methods

This narrative review integrates peer-reviewed original studies, clinical trials, and highquality review articles published predominantly between 2017 and 2025. Literature was selected based on relevance to ALS molecular pathophysiology, targeted therapeutic strategies, biomarker development, and clinical trial methodology. Data were synthesized qualitatively, emphasizing target engagement, biomarker modulation, and translational limitations.

Results

ALS pathogenesis converges on shared downstream mechanisms, including RNA dysmetabolism, impaired proteostasis, mitochondrial dysfunction, and neuroinflammation, despite diverse genetic drivers. Antisense oligonucleotide (ASO) therapies—particularly targeting *SOD1*—have demonstrated robust biological efficacy, including molecular target engagement and neurofilament light chain (NfL) modulation. NfL has emerged as the most robustly validated biomarker for prognosis, patient stratification, and pharmacodynamic assessment, although its predictive value for long-term clinical benefit remains under evaluation. Non–ASO disease-modifying approaches have shown variable clinical outcomes, highlighting methodological and biological challenges.

Conclusions

Disease-modifying intervention in ALS is biologically feasible but remains limited by delayed diagnosis, disease heterogeneity, and conventional trial design constraints. Integration of molecular stratification, biomarker-guided evaluation, and innovative trial methodologies is essential to advance precision therapeutics in ALS.

Key words: Amyotrophic lateral sclerosis, biomarkers, NfL

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons, leading to paralysis, respiratory failure, and death, typically within a few years of symptom onset. Although the clinical phenotype of ALS appears relatively uniform, accumulating evidence indicates that the disease is biologically heterogeneous, encompassing multiple genetic and sporadic subtypes driven by distinct molecular mechanisms that converge on motor neuron degeneration.
Advances in molecular genetics and transcriptomics have identified more than 40 ALSassociated genes, revealing convergent pathogenic pathways involving ribonucleic acid (RNA) metabolism, protein homeostasis, nucleocytoplasmic transport, mitochondrial dysfunction, and neuroinflammation. Pathological aggregation and miss localization of TAR DNA-binding protein 43 (TDP-43) represent a unifying downstream feature in most sporadic and several genetic forms of ALS, supporting the concept of shared molecular endpoints despite diverse upstream triggers. This mechanistic framework has provided a strong rationale for the development of disease-modifying therapies targeting specific molecular drivers of neurodegeneration.

Until recently, therapeutic options in ALS were limited to symptomatic care and modestly effective neuroprotective agents. However, the field has entered a new era with the emergence of molecularly targeted approaches, most notably antisense oligonucleotides (ASOs), which enable sequence-specific suppression of pathogenic transcripts. Clinical trials of ASO therapy in *SOD1*-associated ALS have demonstrated robust target engagement and biomarker modulation, establishing proof of biological efficacy in human ALS.

Concurrently, neurofilament light chain (NfL) has emerged as a validated biomarker reflecting axonal injury, disease activity, and treatment response, transforming both prognostic assessment and clinical trial design. Despite these advances, translation into consistent clinical benefit remains challenging due to delayed diagnosis, disease heterogeneity, and limitations of conventional outcome measures.

This review summarizes contemporary evidence on disease-modifying therapies in ALS, integrating clinical trial data, biomarker insights, and molecular targets to define current progress and future directions toward precision therapeutics.

1.1 Background

Recent advances in molecular neuroscience have reframed ALS as a biologically heterogeneous disorder characterized by convergent pathogenic pathways rather than a single disease entity. Genetic discoveries, coupled with transcriptomic and proteomic analyses, have identified diverse upstream drivers- including mutations affecting RNA-binding proteins, protein quality control systems, and intracellular trafficking- that ultimately converge on motor neuron degeneration. This conceptual shift has directly influenced therapeutic development, prioritizing interventions that target defined molecular mechanisms and enable objective assessment of biological efficacy.

Concurrently, the validation of fluid biomarkers, particularly NfL, has provided critical tools for capturing disease activity and therapeutic engagement. These developments have reshaped the interpretation of clinical trials in ALS, allowing biological effects to be detected even when short-term functional outcomes remain unchanged. As a result, contemporary ALS research increasingly integrates molecular stratification, biomarker-driven endpoints, and mechanistically informed trial designs.

1.2 Methods

This review was conducted as a focused narrative synthesis of peer-reviewed literature addressing disease-modifying therapies in ALS. The primary source material consisted of original research articles, clinical trials, and high-quality review papers provided by the author, encompassing studies published predominantly between 2017 and 2025 in leading neurology and neuroscience journals. These publications were selected based on their relevance to molecular pathophysiology, targeted therapeutic strategies, biomarker development, and clinical trial methodology in ALS.

Emphasis was placed on therapies with a clear mechanistic rationale, including antisense oligonucleotide–based approaches, metabolic and neuroprotective agents, and biomarkerguided interventions. Data were synthesized qualitatively, with particular attention to target engagement, biomarker modulation, clinical outcomes, and limitations identified by study authors. No meta-analytic techniques were applied due to heterogeneity in study designs, populations, and outcome measures.

Interpretation of findings was guided by established clinical and biological knowledge of ALS, with care taken to avoid extrapolation beyond the evidence presented in the source publications.

1.3 Molecular Pathophysiology and Therapeutic Targets in ALS

ALS is currently understood as a biologically heterogeneous disorder in which diverse genetic and environmental factors converge on a limited number of downstream pathogenic pathways leading to motor neuron degeneration. [1–3] Large-scale genetic and genomic studies have identified more than 40 ALS-associated genes, encompassing both familial and sporadic disease, thereby redefining ALS as a spectrum of molecularly distinct subtypes rather than a single nosological entity. [2,3]

A central pathogenic theme emerging from these studies is disruption of RNA metabolism. Many ALS-associated genes encode RNA-binding proteins or regulators of RNA processing, transport, and stability. Among these, TDP-43 occupies a pivotal role. Pathological mislocalization of TDP-43 from the nucleus to the cytoplasm, accompanied by aggregation and loss of normal nuclear function, is observed in the majority of sporadic ALS cases and in several genetic forms, supporting its role as a common downstream effector of neurodegeneration. [2,4] Dysregulated RNA splicing, impaired stress granule dynamics, and altered RNA transport have all been linked to TDP-43 pathology, providing a mechanistic bridge between diverse upstream genetic insults and shared cellular dysfunction. [4]

In parallel, disturbances in protein homeostasis and proteostasis networks represent another convergent pathway in ALS. Impairment of ubiquitin–proteasome and autophagy–lysosome systems contributes to the accumulation of misfolded and aggregation-prone proteins,

exacerbating neuronal vulnerability. [1,2] These defects are closely intertwined with mitochondrial dysfunction, axonal transport failure, and synaptic degeneration, all of which are consistently observed across ALS subtypes. [2]

Neuroinflammatory mechanisms further modulate disease progression. Transcriptomic and pathological studies demonstrate activation of microglia and astrocytes, with a shift toward pro-inflammatory phenotypes that may amplify motor neuron injury, particularly in later disease stages. [1,2] Importantly, these non–cell-autonomous processes provide additional therapeutic entry points beyond neuron-specific targets.

Together, these convergent pathogenic domains- RNA dysmetabolism, proteostasis failure, mitochondrial dysfunction, and neuroinflammation - have directly informed contemporary therapeutic strategies. Rather than targeting ALS as a uniform clinical syndrome, current disease-modifying approaches increasingly focus on precise molecular targets within these pathways, laying the foundation for gene- and mechanism-based interventions. [5,6]

Table 1. Key Genes in ALS Pathogenesis

Gene / protein	Principal pathogenic domain	Verified role in ALS
C9orf72	RNA toxicity, nucleocytoplasmic transport, proteostasis	The most common genetic cause of ALS/FTD; hexanucleotide repeat expansions generate toxic RNA species and dipeptide repeat proteins, disrupt nucleocytoplasmic transport, and alter immune and proteostatic pathways; a major but biologically sensitive target for ASO-based therapies.
SOD1	Proteostasis, oxidative stress	Mutations confer toxic gain-of-function properties and promote protein misfolding and aggregation; represents the most clinically advanced ASO target in ALS, with demonstrated target engagement and neurofilament modulation.
TARDBP / TDP-43	RNA metabolism, protein aggregation	A central downstream effector in the majority of sporadic ALS and several genetic forms; pathological mislocalization and aggregation lead to widespread RNA processing defects and cellular stress.
FUS	RNA metabolism, stress granule dynamics	Mutations disrupt RNA binding and promote abnormal aggregation; associated with ALS subtypes that may exhibit distinct molecular pathology, sometimes without classical TDP-43 inclusions.
ATXN2	Genetic risk modifier, RNA metabolism	Intermediate polyglutamine expansions increase ALS risk; functions as a disease modifier converging on TDP-43–related pathways and represents a promising ASO target beyond monogenic ALS.

TBK1	Autophagy, innate immune signaling	Mutations link impaired autophagic clearance with dysregulated immune responses, highlighting the intersection of neurodegeneration and neuroinflammation in ALS.
OPTN	Autophagy, protein degradation	An autophagy receptor; loss-of-function mutations impair clearance of damaged proteins and organelles, increasing motor neuron vulnerability.
SQSTM1 (p62)	Proteostasis, autophagy	A key autophagy adaptor protein; dysfunction promotes accumulation of misfolded proteins and integrates ALS pathology with broader protein aggregation disorders.
VCP	Proteostasis, ERassociated degradation, autophagy	Mutations disrupt protein degradation pathways and endoplasmic reticulum homeostasis, leading to proteostatic stress and neurodegeneration.
KIF5A	Axonal transport	Mutations impair microtubule-based axonal transport, a critical vulnerability factor for long-projecting motor neurons.

1.4 Biomarkers in Amyotrophic Lateral Sclerosis The development of reliable biomarkers has become a central priority in ALS research, driven by the need to capture disease activity, prognostic heterogeneity, and biological response to therapy in a condition characterized by rapid progression and substantial interindividual variability. [2,5] Traditional clinical outcome measures, including the ALS Functional Rating Scale–Revised (ALSFRS-R), are limited by non-linearity, floor effects, and sensitivity to symptomatic fluctuations, underscoring the need for objective biological markers. [7,8]

Among candidate biomarkers, NfL has emerged as the most extensively validated fluid biomarker in ALS. Neurofilaments are structural components of large-caliber axons, and their release into cerebrospinal fluid and blood reflects the intensity of neuroaxonal injury. [7,8] Multiple studies demonstrate that NfL concentrations are elevated early in the disease course and remain relatively stable thereafter, consistent with a marker of disease intensity rather than cumulative disability. [7]

Importantly, baseline NfL levels are strongly associated with prognosis, with higher concentrations correlating with more rapid functional decline and shorter survival across ALS subtypes. [7,8] This prognostic value is observed in both cerebrospinal fluid and blood-based assays, facilitating broad clinical applicability. [7] These properties position NfL as a robust stratification biomarker for clinical trials, enabling enrichment of study populations and adjustment for biological heterogeneity. [8,9]

Beyond prognosis, NfL has gained increasing relevance as a pharmacodynamic biomarker. Reductions in NfL levels following therapeutic intervention have been interpreted as evidence

of target engagement and attenuation of neuroaxonal injury, even in the absence of immediate clinical benefit. [8] This concept has been particularly influential in the evaluation of molecularly targeted therapies, where biological effects may precede measurable functional change. [8,10]

Recognizing this evidence base, regulatory and translational frameworks have begun to incorporate NfL as a biomarker reasonably likely to predict clinical benefit in ALS, supporting its use in early-phase trials and adaptive study designs. [8] Nevertheless, important limitations remain, including variability across disease stages and the need to contextualize biomarker changes within specific molecular subtypes. [2,5]

Table 2. Key Biomarkers in ALS

Biomarker	**Biological sample**	**Primary biological meaning**	**Verified clinical / translational relevance**
Neurofilament light chain (NfL)	CSF; blood (serum or plasma)	Neuroaxonal injury and disease intensity	The most robustly validated ALS biomarker; elevated early and relatively stable over time; strongly prognostic; widely used for patient stratification and as a pharmacodynamic marker in clinical trials.
Phosphorylated neurofilament heavy chain (pNfH)	CSF; blood	Neuroaxonal damage	Closely related to NfL; demonstrates prognostic value, though with greater variability and less consistent performance than NfL.
CSF SOD1 protein	CSF	Target engagement	Direct pharmacodynamic biomarker in SOD1directed ASO trials; reduction confirms effective suppression of pathogenic SOD1 expression.
Neurofilament change (ΔNfL)	Longitudinal CSF or blood	Treatmentrelated biological response	Decreases following intervention interpreted as evidence of biological activity and attenuation of neuroaxonal injury, even when functional benefit is delayed.
Dipeptide repeat proteins (e.g., poly(GP))	CSF	C9orf72 repeatassociated pathology	Biomarker of repeat-associated translation in C9orf72 ALS; used to confirm biological activity of gene-targeted therapies in translational and early-phase studies.

1.5 Antisense Oligonucleotide–Based Therapies in Amyotrophic Lateral Sclerosis

ASOs represent the most advanced molecularly targeted therapeutic strategy currently investigated in ALS, offering sequence-specific modulation of disease-causing transcripts and direct engagement of defined pathogenic mechanisms. [5,6] ASOs are short, synthetic nucleic acid sequences designed to bind complementary RNA targets, leading to transcript degradation or modulation of RNA processing through well-characterized cellular pathways. [6]

The strongest clinical evidence for ASO therapy in ALS derives from studies targeting *SOD1*, a gene causally linked to a subset of familial ALS. Preclinical investigations demonstrated that suppression of mutant *SOD1* reduces toxic protein accumulation and ameliorates motor neuron degeneration in cellular and animal models, providing a clear mechanistic rationale for clinical translation. [3,6] Subsequent early-phase clinical trials of *SOD1*-directed ASO therapy confirmed robust target engagement, with reductions in cerebrospinal fluid SOD1 protein and associated decreases in NfL, indicating attenuation of neuroaxonal injury. [8,11]

In later-stage clinical evaluation, *SOD1* ASO therapy demonstrated clear biological activity but more modest and delayed clinical effects, highlighting the temporal dissociation between biomarker modulation and functional outcomes in ALS. [10,11] These findings reinforced the concept that molecular intervention may be most effective when initiated early in the disease course, prior to extensive and irreversible motor neuron loss. [5,11] Longitudinal analyses further suggested that sustained target suppression is required to maintain biological effects, underscoring the chronic nature of disease-modifying treatment in ALS. [11]

Beyond *SOD1*, ASO strategies targeting other genetic forms of ALS, including *C9orf72*, *FUS*, and modifiers such as *ATXN2*, have demonstrated promising preclinical results by reducing toxic RNA species, abnormal protein products, or downstream TDP-43 pathology. [1,4,6] However, translation of these approaches into human trials has proceeded cautiously, reflecting concerns regarding the physiological roles of certain targets- particularly *C9orf72*- and the potential consequences of excessive transcript suppression. [1,4]

Collectively, ASO-based therapies have established proof of biological efficacy in ALS and validated molecular target engagement as a feasible therapeutic strategy. At the same time, their clinical development has exposed fundamental challenges, including optimal timing of intervention, patient stratification, and the interpretation of biomarker-driven outcomes in a clinically heterogeneous disease. [5,10]

1.6 Non–ASO Disease-Modifying Therapies in ALS

In parallel with gene-targeted approaches, several non–ASO disease-modifying strategies have been explored in ALS, aiming to modulate downstream pathogenic pathways shared across genetic and sporadic forms of the disease. These approaches primarily target mitochondrial dysfunction, endoplasmic reticulum stress, neuroinflammation, and impaired cellular resilience, reflecting insights derived from convergent pathophysiological mechanisms. [1,2]

Metabolic and neuroprotective therapies have received particular attention due to their potential applicability across ALS subtypes. Agents designed to stabilize mitochondrial function and reduce cellular stress responses demonstrated biological plausibility and early clinical signals, though subsequent evaluation revealed substantial variability in clinical outcomes. [2,5] The interpretation of these findings has been complicated by disease heterogeneity, short trial durations, and reliance on functional endpoints with limited sensitivity to early biological effects. [9,10]

Neuroinflammatory pathways represent another important therapeutic target in ALS. Transcriptomic and pathological studies consistently demonstrate activation of innate immune signaling, including microglial and astrocytic responses, which may contribute to non–cellautonomous motor neuron injury, particularly in later disease stages. [1,2] Pharmacological modulation of neuroinflammation has therefore been investigated as a potential diseasemodifying strategy, although clinical translation has been challenged by difficulties in patient selection, target engagement assessment, and disentangling neuroprotective effects from symptomatic modulation. [5,9]

Cell-based therapies have also been evaluated as a means of enhancing neuroprotection and modifying the disease environment. Early-phase clinical studies have primarily focused on safety and feasibility, demonstrating acceptable tolerability but inconsistent or modest signals of efficacy. [1,2] The absence of validated biomarkers of biological response has further limited interpretation of these trials and hindered optimization of dosing and patient stratification. [8]

Across these non–ASO approaches, a recurring theme is the dissociation between biological rationale and reproducible clinical benefit. These experiences underscore the limitations of traditional trial designs in ALS and reinforce the need for biomarker-guided evaluation, molecular stratification, and integration of biological endpoints alongside functional measures. [5,9,10]

1.7 Clinical Trial Design in Amyotrophic Lateral Sclerosis

The design of clinical trials in ALS presents unique methodological challenges arising from rapid disease progression, substantial biological heterogeneity, and delayed diagnosis, all of which limit the window for effective disease-modifying intervention. [2,5] Epidemiological and natural history studies indicate that most patients are enrolled months after symptom onset, at a stage when a significant proportion of upper and lower motor neurons has already been lost, thereby constraining the capacity of targeted therapies to translate biological effects into measurable clinical benefit. [2,3,5]

Historically, ALS clinical trials have relied heavily on functional outcome measures, most prominently the ALSFRS-R. Although ALSFRS-R remains the most widely used clinical endpoint, it is limited by non-linearity, ceiling and floor effects, and vulnerability to symptomatic and supportive care–related fluctuations, which collectively reduce sensitivity to early or modest biological treatment effects. [2,9,10] These limitations have contributed to a recurrent discordance between biological activity- demonstrated through molecular target engagement or biomarker modulation- and short-term functional outcomes, particularly in trials of gene- and mechanism-targeted therapies. [5,10,11]

Recent methodological advances increasingly emphasize the integration of biomarkers into ALS trial design as tools for patient stratification, prognostic enrichment, and

pharmacodynamic assessment. NfL has emerged as the most robustly validated biomarker in this context, providing an objective measure of neuroaxonal injury that is relatively independent of transient clinical fluctuations. [7,10] Incorporation of NfL into early-phase trials enables detection of biological effects even when functional change is not immediately apparent and may facilitate more efficient evaluation of candidate therapies. [8,9]

In parallel, adaptive and platform trial designs have gained increasing attention as strategies to address inefficiencies inherent in conventional randomized controlled trials in ALS. These designs permit simultaneous evaluation of multiple interventions, response-adaptive randomization, and early discontinuation of futile treatment arms, thereby reducing patient exposure to ineffective therapies and accelerating signal detection. [5,9,12] Collectively, these developments reflect a broader shift toward biologically informed, mechanism-driven trial paradigms that align therapeutic evaluation with the molecular and clinical heterogeneity of ALS. [2,5]

1.8 Translational Barriers and Future Directions

Despite substantial advances in molecular understanding and therapeutic development, translation of biological insights into consistent clinical benefit in ALS remains limited. A central barrier is the profound heterogeneity of ALS at genetic, molecular, and clinical levels, which complicates patient selection and dilutes treatment effects in unstratified trial populations. [2,5] This heterogeneity challenges traditional trial paradigms and underscores the inadequacy of "one-size-fits-all" therapeutic approaches in a disease increasingly recognized as a spectrum of biologically distinct subtypes rather than a single entity.

Another critical obstacle is the temporal mismatch between disease biology and clinical intervention. Molecular, genetic, and biomarker studies indicate that key pathogenic processes are active well before clinical diagnosis, suggesting that treatment initiation often occurs after substantial and irreversible motor neuron loss has already taken place. [3,11,13] Experience from gene-targeted therapies, particularly *SOD1* ASO trials, further illustrates that biological target engagement may precede measurable functional benefit by many months, reinforcing the rationale for earlier intervention strategies. [10,11] These observations support the exploration of presymptomatic or very early symptomatic treatment in genetically defined populations, coupled with biomarker-based monitoring of disease activity. [8,11]

Interpretation of biomarker dynamics represents an additional translational challenge. Although reductions in NfL provide compelling evidence of biological activity and target engagement, the quantitative relationship between biomarker modulation and long-term clinical benefit remains incompletely defined. [5,8] This uncertainty complicates regulatory decision-making and highlights the need for longitudinal validation of biomarkers as surrogate endpoints across diverse ALS subtypes. [7,10]

Methodological analyses and trial innovation studies further emphasize that many historical failures in ALS drug development reflect limitations of trial design rather than absence of biological effect. [9] Proposed solutions include enrichment strategies based on molecular or biomarker profiles, incorporation of pharmacodynamic endpoints, and adoption of adaptive and platform trial architectures that allow more efficient signal detection and iterative learning. [1,9]

These approaches aim to align trial methodology with the pace and complexity of modern ALS biology.

Looking forward, progress in ALS therapeutics will likely depend on integrated precision medicine strategies combining molecular stratification, biomarker-guided evaluation, and rational combination therapies targeting multiple pathogenic pathways simultaneously. [1,2] Advances in genetic screening, longitudinal biomarker monitoring, and innovative trial designs provide a credible framework for translating mechanistic insight into durable clinical benefit, although careful validation and cautious interpretation will remain essential.

2. **Research objective**

The objective of this review was to synthesize contemporary evidence on disease-modifying therapies in amyotrophic lateral sclerosis, with a particular focus on molecularly targeted interventions, validated biological biomarkers, and clinical trial methodologies. The review aimed to integrate insights from genetic, molecular, and biomarker research to evaluate current therapeutic progress, identify translational limitations, and outline future directions toward precision medicine approaches in ALS.

3. Research materials and methods

3.1. Literature search strategy

This narrative review was based on peer-reviewed original research articles, clinical trials, and authoritative review papers addressing disease-modifying therapies in amyotrophic lateral sclerosis. The primary source material consisted of publications provided by the author, supplemented by established biomedical knowledge in the field of ALS. The included literature was published predominantly between 2017 and 2025 in leading neurology and neuroscience journals. **3.2. Eligibility criteria**
Studies were selected based on relevance to ALS molecular pathophysiology, gene- and mechanism-targeted therapeutic strategies, biomarker development, and clinical trial methodology. Both preclinical and clinical studies were considered when they provided translational insight into therapeutic mechanisms or biomarker validation. Articles focusing exclusively on symptomatic treatment without mechanistic relevance were excluded.

3.3. Data extraction and synthesis

Relevant data were extracted qualitatively, with emphasis on molecular targets, biological mechanisms, biomarker performance, clinical trial outcomes, and limitations identified by study authors. Findings were synthesized narratively to highlight convergent pathogenic pathways, therapeutic strategies, and translational challenges. No quantitative meta-analysis was performed due to heterogeneity in study design, patient populations, and outcome measures.

3.4. Artificial intelligence (AI) support

Artificial intelligence - based language support tools were used to assist in linguistic editing and structural organization of the manuscript. All scientific interpretation, data synthesis, and conclusions were performed by the authors, who take full responsibility for the accuracy and integrity of the content.

4. Discussion

This review highlights the profound shift that has occurred in ALS research over the past decade, moving from empiric, largely symptomatic treatment strategies toward biologically informed, mechanism-driven therapeutic development. Insights from genetic, molecular, and biomarker studies have established ALS as a heterogeneous disorder characterized by convergent pathogenic pathways, providing a conceptual framework for disease-modifying intervention. [1-3]

Among emerging therapeutic strategies, antisense oligonucleotide - based approaches represent the most mature example of molecular precision medicine in ALS. Clinical development of *SOD1* - directed ASO therapy has demonstrated unequivocal target engagement and reproducible biomarker modulation, establishing proof of biological efficacy in human disease. [8,11] However, the delayed and modest clinical effects observed in later - stage trials underscore a central challenge in ALS therapeutics: the dissociation between biological activity and measurable functional benefit when intervention is initiated after substantial motor neuron loss. [10,11] These findings reinforce the importance of early intervention and molecular stratification.

The emergence of NfL as a validated biomarker has fundamentally altered the interpretation of ALS trials. NfL provides objective insight into disease intensity and treatment - related biological effects, addressing key limitations of traditional functional endpoints. [7,8] Nevertheless, uncertainty remains regarding the extent to which biomarker modulation predicts long - term clinical benefit, emphasizing the need for continued longitudinal validation and cautious regulatory interpretation. [5,10]
Experience with non-ASO disease - modifying therapies further illustrates the complexity of ALS translation. Despite strong mechanistic rationale, metabolic, neuroprotective, anti - inflammatory, and cell-based approaches have produced inconsistent clinical outcomes, often limited by heterogeneity, suboptimal patient selection, and insufficient biomarker integration. [2,5,9] Collectively, these challenges highlight the inadequacy of uniform therapeutic approaches in a biologically diverse disease.

5. Conclusion

Contemporary ALS research has entered a new era defined by molecular characterization, biomarker validation, and targeted therapeutic development. Evidence synthesized in this review demonstrates that disease - modifying intervention in ALS is biologically feasible, as exemplified by antisense oligonucleotide therapies and biomarker - driven trial paradigms. At the same time, translation into consistent clinical benefit remains constrained by delayed diagnosis, disease heterogeneity, and limitations of conventional outcome measures.

Future progress will depend on integrating molecular stratification, early intervention, and biomarker - guided trial designs to align therapeutic strategies with underlying disease biology. Advances in genetic screening, longitudinal biomarker monitoring, and adaptive clinical trial methodologies provide a realistic pathway toward precision medicine in ALS. While substantial challenges remain, the convergence of mechanistic insight and translational innovation offers a credible foundation for transforming ALS from a uniformly fatal disorder into a biologically tractable disease with personalized therapeutic options.

Disclosures

Author's contribution:
Conceptualization: WP, BP, NMK; Methodology: WP, JAW, MMT, LO; Software: WP, AP, JP; Check: AG, AK; Formal analysis: BP, NMK, AP; Investigation: AG, LO, AK; Resources: JAW, MMT; Data curation: WP, BP, JP; Writing-rough preparation: MMT; Writing -review and editing: NMK, BP, JAW, AG; Visualization: JP, AP, LO; Supervision: WP, AK, MMT; Project administration: NMK, WP, JAW

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