AWARD FOR BEST RESEARCH PRESENTATION AT THE WCMSR ORIGINAL RESEARCH BASED ON JUDGE SCORES, 2ND PLACE

32. UNDERSTANDING THE ROLE OF INFLAMMATION IN ALS-FTSD: A SYSTEMATIC REVIEW AND META-ANALYSIS INVESTIGATING THE RELATIONSHIP BETWEEN INFLAMMATION AND AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL SPECTRUM DISORDER

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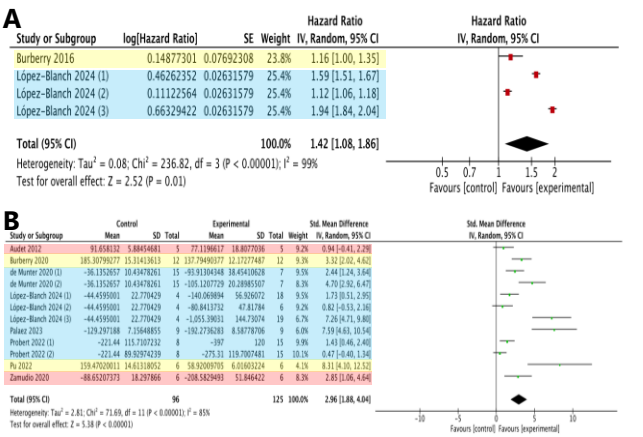
https://www.youtube.com/live/fSpXH-3Xy5w?t=24111s

BACKGROUND: Amyotrophic lateral sclerosis (ALS) is a rare, severely debilitating neurodegenerative disease characterised by progressive degeneration of upper and lower motor neurons. More than 50% of those affected also exhibit characteristic frontotemporal dementia (FTD) symptoms. Therefore, it is now widely recognised as a spectrum disorder encapsulating both motor and cognitive deficits, termed Amyotrophic lateral sclerosis frontotemporal spectrum disorder (ALS-FTSD). While the pathophysiology is poorly understood, a growing body of literature demonstrates the involvement of inflammation in ALS-FTSD. This systematic review and meta-analysis investigated the role of inflammation in ALS-FTSD and answer the question of whether interventions targeting inflammation will improve survival and motor outcomes through multiple biochemical pathways across the genetic and pathological spectrum of ALS-FTSD. **METHODS:** Three databases, (1) PubMed, (2) Ovid-Medline, and (3) Ovid-Embase, were searched using predetermined search terms. After Screening, 1,302 papers underwent data extraction and categorisation. These informed our choice to investigate in-depth, drug intervention studies targeting inflammation in relatively understudied preclinical genetic mouse models of ALS-FTSD. Of 53 potential papers identified, nine were meta-analysed quantitatively, yielding four interventions targeting inflammatory pathways which reported survival, and 12 interventions reporting rotarod latency to fall, a commonly reported motor phenotype. **RESULTS:** Following an overview of the current state of the research field, a specific focus of quantitative and qualitative analysis was determined. It was found that the SOD1 genetic mouse model are overrepresented and given that a published meta-analysis has already been carried out looking into therapeutic interventions on several physiological targets, including inflammation. It was decided to focus on the relatively understudied but incredibly clinically relevant TDP-43, C9orf72, and FUS mouse models for meta-analysis, which are more representative of human pathology than SOD1. Meta-analysis of the overall effect of inflammation-targeted interventions on survival in ALS-FTSD mouse models produced a hazard ratio of 1.42 (95%CI 1.08 to 1.86), with a Z-score of 2.52 (p=0.01), demonstrating inflammation-targeted interventions have a statistically significant positive effect on survival in ALS-FTSD mouse models. Meta-analysis of the overall effect of inflammation-targeted interventions on motor function in ALS-FTSD mouse models produced a standardised mean difference of 2.96 (95%CI 1.88 to 4.04), with a Z-score of 5.38 (p<0.00001), demonstrating that inflammation-targeted interventions have a statistically significant positive effect on motor function in ALS-FTSD mouse models. **CONCLUSION:** The results of this meta-analysis demonstrate that interventions which decrease inflammation have significant positive effects on both survival and motor symptoms compared to controls in mouse ALS-FTSD model studies. This evidence demonstrates that inflammation is a crucial driver of the ALS-FTSD disease process although further investigation is required to fully characterise the nature of their mechanisms, side effects, and efficacy in human disease. Moving forward, the most challenging aspect of future research will be bridging the translation gap between preclinical studies and effective human therapeutics. This review suggests that interventions targeting inflammation are a promising avenue for future therapeutic research and development.

Figure: (A) Survival Hazard Ratios and (B) Motor Function Improvements with Inflammation-Targeted Therapeutics in Amyotrophic Lateral Sclerosis–Frontotemporal Spectrum Disorder Mouse Models.



Legend: (A) Forest plot illustrating the hazard ratio for survival between experimental (intervention) and control groups in ALS-FTSD mouse models. Data are presented using an inverse variance random-effects model with a 95% confidence interval (CI). The black diamond represents the overall effect, demonstrating a statistically significant improvement in survival for the intervention group. (B) Forest plot displaying the standardized mean difference (SMD) in rotarod fall latency time between experimental and control groups in ALS-FTSD mouse models. Data are presented using an inverse variance random-effects model with a 95% CI. The black diamond indicates a statistically significant improvement in motor function for the intervention group. Red highlights represent TDP-43 genetic models, yellow represents C9orf72 models, and blue represents FUS models.

Key Words: ALS, Inflammation, C9orf72, FUS Protein, Proteinopathy TDP43.