Not Only about the Drugs: Improved Survival with Noninvasive Ventilation in Amyotrophic Lateral Sclerosis

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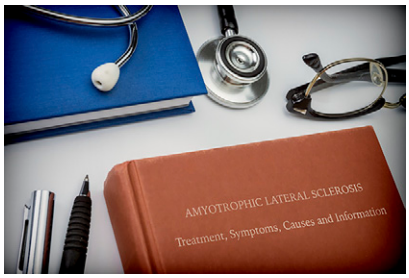
Motor neuron disease or amyotrophic lateral sclerosis (ALS) is a rare, progressive, terminal neurological disease that can strike anyone. As ALS progresses, respiratory muscle strength declines, ventilatory capacity diminishes, and respiratory failure and death ensue. Noninvasive ventilation (NIV) has been a key element of multidisciplinary care since the 2006 randomized controlled trial (RCT) of NIV in 41 people with ALS demonstrated a median survival benefit of 7 months (1). There is now no clinical and/or ethical equipoise to repeat the experiment despite the very real risk that the initial finding was a type 1 error. Five participants died within days of randomization, separating the survival curves very early and likely contributing to the observed benefit. Despite no confirmatory RCTs, numerous subsequent cohorts and case series have associated NIV with increased survival in ALS, and in this issue of *AnnalsATS*, Ackrivo and colleagues (pp. 486–494) have furthered our understanding of the magnitude of benefit with a careful and thorough interrogation of their single-site, 9-year cohort (2).



From a clinic population of 864, Ackrivo and colleagues extracted 452 participants into 180 matched groups; the authors carefully matched people using NIV to the non-NIV group across diagnosis delay, symptom onset site (limb or bulbar), ALSFRS-R orthopnea score >2 or ⩽2 (ALS Functional Rating Scale–Revised), and forced vital capacity percent predicted normal. Immortal time bias was matched for by including the time since the first visit to the day of matching. Once matched, both unadjusted and adjusted survival were modeled and reported taking into account the known confounders of age at diagnosis, body mass index, ALSFRS-R dyspnea score, and daily hours of NIV use.

The NIV users had an unadjusted median survival of 8.0 months from NIV prescription versus 7.4 months for the people who did not receive NIV. This difference equated to a 20% nonsignificant reduction in the rate of death, which rose to 26% and became statistically significant once known confounders were controlled for (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.57–0.98; $P = 0.04$). As the authors noted, another large cohort from our group demonstrated a very similar adjusted HR of 0.72 (95% CI, 0.60–0.88) (3). Our paper reported a median survival advantage of 13 months from a different baseline (symptom onset vs. time of NIV initiation), and although we addressed left-truncation in our cohort, Ackrivo and colleagues arguably better controlled for immortal time bias in their analyses (2). Ackrivo and colleagues also refined their model in a secondary analysis of time-matched groups by diagnostic delay and follow-up time since first visit, and this further extended the reduction in the rate of death (HR, 0.61; 95% CI, 0.46–0.82; $P = 0.001$). Other cohorts have reported a range of survival benefits with NIV from different baselines; Lo Coco and colleagues reported a median survival advantage from disease onset of 18 months (4), whereas Kleopa and colleagues (5) and Aboussouan and colleagues (6) both reported their survival advantages from time of NIV prescription in those adherent with therapy as 10 and 15 months, respectively.

Alongside the carefully controlled analyses of whether NIV increases survival time overall, Ackrivo's team also examined whether the amount of NIV use matters. After adjustment for body mass index and age at diagnosis, the authors showed that >4 h/d was associated with a 33% reduction in the rate of death (median, unadjusted survival of 10.7 months in >4 hours vs. 5.9 months in users of <4 h/d). This "dose–response" on survival has been similarly observed by other groups; the median survival was 18.0 months if >4 h/d versus 6 months if <4 h/d and 14.2, 7.0, and 4.6 months if >4 h/d, <4 h/d, or refused NIV, respectively (4, 5). In a previous physiological study from an unselected NIV cohort, it was found that greater NIV usage per day better controls arterial carbon dioxide and sleepiness and that the "effective dose" cutoff is >4 h/d (7). Furthermore, a recent single-site randomized controlled trial determined that careful alignment of NIV settings to patient effort using an overnight sleep study can increase adherence with NIV in ALS. In participants who initially used NIV for <4 h/d, optimizing NIV increased adherence by 118 minutes (95% CI, 53–182; $P < 0.01$) compared with control subjects (8). NIV use in ALS is recommended in clinical guidelines globally (9), but only recently has literature emerged that highlights the importance of the quality of NIV care and the need for ongoing alignment of care with symptom relief and clinical needs (10).

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Sleep disordered breathing in ALS is a potent source of repeated sleep fragmentation, chronic intermittent hypoxia (CIH), and reperfusion (8). These reperfusion events are strongly associated with the generation of intracellular reactive oxygen species and alterations in cellular redox status (11). Oxidative stress has been identified as a therapeutic target in ALS (12), and a recent animal model has demonstrated a potential link between sleep disordered breathing and ALS progression (13). ALS mice (SOD1-G93A) and wild-type control mice (Wt) were randomized to CIH or normoxia (NOX) for 12 hours during sleep over 2 weeks. In the CIH-exposed ALS mice, motor learning on the rotarod test ($P = 0.017$), spatial memory ($P = 0.016$), and wire hanging ($P = 0.037$) were all statistically impaired compared with the ALS-NOX conditions and worse than Wt-NOX and Wt-CIH, although not always statistically different (13). Furthermore, CIH in an optineurin-deficient ALS mouse model (optineurin appears to be relatively respiratory neuroprotective in humans with ALS) accelerates ventilatory decline (14). These data suggest that NIV could provide relief from repeated sleep fragmentation, CIH, and reperfusion "upstream" of end-organ and cellular dysfunction in ALS and thus potentially modify or potentiate cellular therapies.

In the original Riluzole study (15), the uncontrolled median 12-month survival advantage was 39%, but if we look at a comparison time at the end of the placebo-controlled period, a time more aligned to the NIV survival literature, the advantage was 19% or 2.8 months, an estimate at the lower end of the benefits reported with NIV. Furthermore, when the original Riluzole dose-finding study were reexamined, it was apparent that the bulk of the survival benefit from Riluzole accrues in stage 4 of the disease; the clinical period characterized as that when a person achieves clinical readiness for NIV (16). The original Riluzole study (15) did not control for NIV prescription or adherence, and although randomization should have accounted for group allocation (chance) differences, it is interesting to speculate whether uncontrolled benefits from therapies such as NIV may have confounded the results. As such, we believe that an important conclusion to draw from studies such as that by Ackrivo and colleagues is that NIV prescription and actual adherence with therapy in hours is a critical confounder that must be measured in future trials of ALS therapeutics, particularly as we move toward large-scale and platform trials such as TRICALS (17) and HEALEY (clinical trials number NCT04297683).

We can never undertake another RCT of NIV versus no NIV, but the data from the five cohorts clearly indicate that NIV increases survival if you can use it, and emerging preclinical data may suggest that NIV is disease modifying per se. The challenge is to both increase uptake of NIV from clinician prescription through to patient use and family support and to drive comprehensive clinical and basic science partnerships that fully explore how and where the prescription of NIV sits in the disease process. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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