Current Clinical Trials Shaping Future Directions in ARDS

Written by Mary Beth Nierengarten

Much investigation is ongoing to improve monitoring and therapeutic options for acute respiratory distress syndrome (ARDS), with more than 300 trials currently underway.

Niall D. Ferguson, MD, Critical Care Medicine, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada, discussed specific areas of research that are likely to shape our understanding and treatment of ARDS over the next 10 years. Table 1 lists the various issues discussed and their challenges.

Table 1. ARDS Issues: Areas of Research and Challenges

Areas of Research	Challenges
New monitoring devices	
Electrical impedance tomography Extravascular lung water measurement Specific elastance measurement PET scanning Lung ultrasound	These devices are not therapeutic but rather diagnostic and monitoring tools. Therefore, it is important to ensure that the devices are sensibly incorporated into practice and coupled with a therapeutic strategy.
New therapeutic devices—new modes of ventilation	
NAVA, PAV, BiLevel/APRV ECMO ECCO2R	Recent focus is on patient-driven ventilation modes. More data are necessary on the role of ECMO in ARDS, and while ECCO2R is feasible, the appropriate target population is yet to be determined.
New therapeutics and diagnostics	
Steroids Mesenchymal stem cells Specific anti-inflammatories (eg, anti–tissue factor Ab) Biomarkers (sRAGE, VEGF, sTREM, Ang2)	There have been failures to translate basic science to the bedside, with promising basic science results culminating in negative clinical trials.
Novel applications	
ARDS prevention PEEP settings and titration Noninvasive ventilation Neuromuscular blockers Spontaneous breathing in ARDS	A specific area of interest—the potential benefit of higher PEEP—is being studied in 2 trials: Alveolar Recruitment for Acute Respiratory Distress Syndrome [ART; NCT01374022] and Permissive, Hypercapnia, Alveolar Recruitment and Limited Airway Pressures [PHARLAP; NCT01667146].

APRV=airway pressure release ventilation; ARDS=acute respiratory distress syndrome; ECCO2R=extracorporeal carbon dioxide removal; ECMO=extracorporeal membrane oxygenation; NAVA=neurally adjusted ventilated assist; PAV=proportional assist ventilation; PEEP=positive-end expiratory pressure; PET=positron emission tomography.

In addition to these areas of interest, Dr. Ferguson highlighted the need for improved definitions for ARDS. He speculated that the failures of basic science translation may be due to application of therapeutics to heterogenous populations based on inadequate definitions and disease characterization. He stressed the need to make periodic revisions to the syndromic definitions, gradually incorporating basic science with maintenance of the genotype-phenotype link. He also emphasized the need for a large observational study of acute respiratory failure to further define ARDS and large, collaborative, randomized, controlled trials based on sound physiology.

Finally, Dr. Ferguson stated that there is a need for worldwide collaboration to plan for unpredictable and global events, such as severe acute respiratory syndrome. He highlighted the importance of larger trials to help plan for such events, and he cited a global initiative, InFACT, that is taking the lead in this arena.

In summary, ARDS is the subject of intense investigation on many fronts, from improved definitions to diagnostic tools to therapeutic options. As such, the research community is hopeful that these efforts will translate to meaningful advances in the identification and management of ARDS over the next decade.

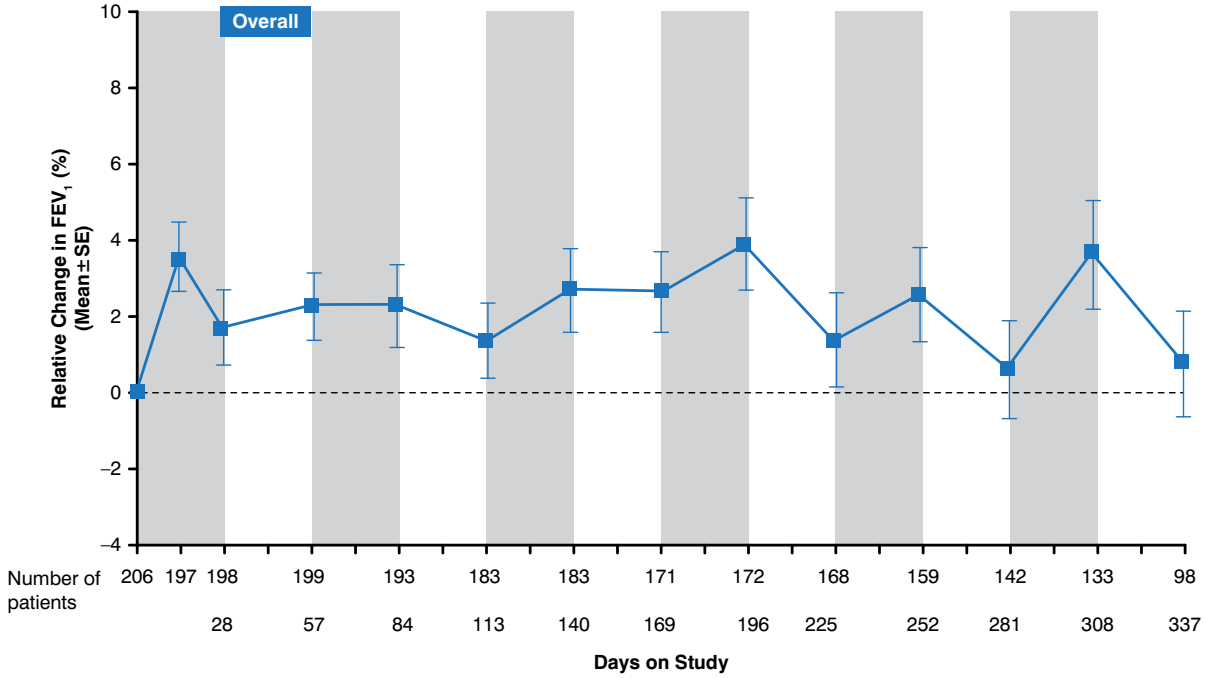
LAI Improves Pulmonary Function in CF

Written by Emma Hitt Nichols, PhD

Treatment of chronic bronchopulmonary infection by *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) with liposomal amikacin for inhalation (LAI) resulted in improved pulmonary function and decreased *P aeruginosa* sputum concentration in an interim analysis. Diana Bilton, MD, Royal Brompton Hospital, London, United Kingdom, presented interim data from the Long Term Safety and Tolerability of Open-Label Liposomal Amikacin for Inhalation in Cystic Fibrosis Patients With Chronic Infection due to *Pseudomonas aeruginosa* trial [CLEAR-110; NCT01316276; Bilton D et al. *Am J Respir Crit Care Med* 2014].

The study treatment consists of amikacin formulated within biocompatible liposomes of about 0.3 μm, which are able to penetrate the biofilm formed by *P aeruginosa* and nontuberculous mycobacteria. The CLEAR-108 study showed that LAI treatment resulted in similar forced expiratory volume in 1 second (FEV_1) in patients with cystic fibrosis and chronic *P aeruginosa* infection as compared with tobramycin inhalation solution (TIS). Patients who completed CLEAR-108 were eligible to

Figure 1. Effect of Long-Term LAI Treatment on FEV_1



Note: Shaded regions represent 28 days on-treatment; dashed line represents baseline.
FEV_1=forced expiratory volume in 1 second; LAI=liposomal amikacin for inhalation.
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enroll in the extension study, CLEAR-110. The purpose of the CLEAR-110 study was to determine the long-term safety and efficacy of LAI.

In CLEAR-110—a multicenter, open-label, Phase 3 study—206 patients aged ≥6 years received 6 cycles of LAI (28 days on, 28 days off) in the first extension and an additional 6 cycles in the second extension. Patients were assessed monthly by the Cystic Fibrosis Questionnaire–Revised, colony-forming units, need for antibiotic rescue treatment, pulmonary exacerbation, and hospitalizations. The patients had a mean age of 21 years and a mean FEV_1 percent predicted of 65.5.

The primary outcome measures were the relative change in FEV_1 and FEV_1 percent predicted, the incidence of treatment-emergent adverse events, and acute tolerability. Secondary efficacy outcomes included a relative change in FEV_1 and FEV_1 percent predicted, time to first protocol-defined pulmonary exacerbation, time to first antipseudomonal antibiotic treatment, shift in minimum inhibitory concentration, and evaluation of emergent pathogens.

Common (>10%) treatment-related adverse events included infective pulmonary exacerbations of cystic fibrosis, nasopharyngitis, upper respiratory tract infection, hemoptysis, cough, and dysphonia. Most adverse events were mild to moderate in severity, and none of the patients receiving LAI discontinued the study drug due to treatment-related adverse events.

Treatment with LAI resulted in a sustained improvement in FEV_1 from baseline over the study period (Figure 1). In addition, patients enrolled in CLEAR-110 who had received TIS in the CLEAR-108 trial showed an increase in FEV_1. Similarly, patients who had received LAI in the CLEAR-108 trial experienced sustained improvement in FEV_1 during LAI treatment in the CLEAR-110 trial.

The density of *P aeruginosa* in sputum appeared to generally decrease from baseline levels, regardless of treatment assignment in CLEAR-108.

In conclusion, Dr. Bilton stated that, in her opinion, the data from the CLEAR-110 extension trial suggest that LAI was well tolerated in patients with cystic fibrosis and chronic infection by *P aeruginosa*. In addition, LAI treatment may improve long-term pulmonary function. Dr. Bilton also pointed out that this interim analysis did not include the entire study population, as the trial is ongoing; therefore, conclusions of the data cannot yet be determined.