detailed information will also likely impact patient outcomes. Finally, this study suffers from underpowering, as it includes just 102 samples, less than half of which are the preinvasive AIS/MIA lesions of interest. Atypical alveolar hyperplasia, a presumed precursor of AIS, was not studied. Indeed, given the extensive genomic changes found in AIS/MIA, to truly understand early carcinogenesis, future studies must consider looking back to earlier preinvasive lesions, and even to the "normal" airways of smokers, as has been done in other tissues (14).

Nevertheless, this study presents one of the largest cohorts published to date of preinvasive lung ADC, a rare disease state that is of great scientific interest given what it can teach us about cancer development. Several putative pathways for carcinogenesis are identified, providing candidates for experimental validation, and the implications for screening, diagnosis, and detection are significant. By stepping backward from invasive cancer into the earliest stages of carcinogenesis, this study represents an important step forward in our understanding of lung cancer evolution. ■

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An Event-driven Trial for Oral Treprostinil
Progress but Not the Holy Grail

Treatment of pulmonary arterial hypertension (PAH) with prostacyclin pathway agents is widely perceived among providers to be the most efficacious treatment compared with treatments acting via other implicated disease pathways such as nitric oxide–cyclic GMP and endothelin. In 1995, intravenous epoprostenol was the first specific PAH therapy approved by the U.S. Food and Drug Administration (FDA), based on a randomized controlled trial demonstrating improvement not only in 6-minute-walk distance (6MWD) but also in mortality compared with controls (1). In 2002, subcutaneous treprostinil (TRE), a prostacyclin analog with a considerably longer half-life (approximately 4 h) than epoprostenol (approximately 6 min), was approved on the basis of a small (16 m), but statistically significant, improvement in 6MWD compared with controls (2). Intravenous TRE was approved in 2004 on the basis of uncontrolled trials showing improved 6MWD in patients started *de novo* on intravenous TRE (3) and maintenance of benefit in patients switched from epoprostenol to TRE (4).

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For years, a key goal of prostacyclin therapy in PAH has been to find an agent with a route of administration that avoids the risks of intravenous therapy (line sepsis and sudden discontinuation) and encumbrances of subcutaneous therapy (high prevalence of site pain). Inhaled prostacyclins have been available for years: iloprost (approved in 2004 in the United States) and TRE (2009). However, the former requires at least six and the latter four administrations daily, and both require fairly complicated and inconvenient devices for administration. Furthermore, perhaps because of frequently missed doses, the inability to titrate dose above certain levels, and/or the inevitable subtherapeutic trough levels that frequently occur during administration, efficacy appears to be less than with either of the infusion routes (5).

In 2013, the FDA approved the first oral prostacyclin, TRE, based on a 23-m improvement in 6MWD in the 12-week FREEDOM M (monotherapy) trial (6), despite the fact that in two combination trials (FREEDOM C and FREEDOM C2), oral TRE failed to significantly increase 6MWD (11 and 10 m, respectively) (7, 8). These failures were thought to be a result of suboptimal dosing in the former trial (FREEDOM C) and a high prevalence of patients receiving dual background therapy (40%) in the latter (FREEDOM C2). In all three studies, dose uptitration was challenging because of the frequency of adverse effects (headache in 70% and gastrointestinal in 40–50%), which was double the occurrence in the placebo groups.

On the basis of findings of the GRIPHON (Prostacyclin Receptor Agonist in Pulmonary Arterial Hypertension) trial (9), the FDA in 2015 approved the oral prostacyclin receptor agonist, the nonprostacyclin selexipag. This event-driven trial of 1,156 patients demonstrated a 40% decrease in the rate of adverse events compared with placebo, mainly disease progression and hospitalizations. Results were similar regardless of background therapy, with 20% of patients receiving no therapy, 47% receiving monotherapy, and 33% receiving dual background therapy. Interestingly, despite the marked reduction in morbid events, the 6MWD at 26 weeks was only 12 m greater in treated patients than in the placebo group.

In this issue of the *Journal*, White and colleagues (pp. 707–717) (10) report findings of the international FREEDOM EV (event) trial that evaluated the effect of oral TRE in patients with PAH recently started on monotherapy with a phosphodiesterase 5 inhibitor or endothelin receptor antagonist (median, 5.4 mo of treatment before enrollment). Enrollment was stopped at 690 patients when the targeted number of events (n = 205) was approached. The median time to the first clinical worsening event, the primary endpoint, was 46 weeks in the TRE group compared with 37 weeks in the control group. The hazard ratio was 0.74 favoring oral TRE, a 26% reduction in the rate of events compared with placebo.

Secondary endpoints including N-terminal-pro brain natriuretic peptide, World Health Organization functional class, 6MWD (22 m improvement over placebo at Week 24 [$P < 0.002$]), and Borg dyspnea score were also significantly improved. A reason posited for the better outcome in the FREEDOM EV trial compared with the earlier FREEDOM C trials was that in the FREEDOM EV trial, oral TRE was dosed thrice daily, as opposed to twice daily in the FREEDOM C trials. The authors speculate that the more frequent dosing permits more stable levels, avoiding peaks that contribute to adverse effects and low troughs that diminish efficacy. Also, even though each dose is less, the greater number of daily doses permits achievement of a higher total daily dose.

Strengths of the FREEDOM EV study include the event-driven design, adequate statistical power, and adjudication of events by an independent committee. The significant improvements in a number of the secondary endpoints also strengthens the credibility of the positive primary endpoint. The findings demonstrate that oral TRE, similar to selexipag, has a sustained effect on the occurrence of morbid events such as disease progression, even with background monotherapy. These findings, however, cannot be extrapolated to dual background therapy (as in the GRIPHON trial). The 26% reduction in the rate of clinical worsening with oral TRE is less than the 40% reduction for selexipag in the GRIPHON trial, but becomes similar (39%) when adjusted for the greater occurrence of baseline risk factors in the TRE versus the placebo group of the FREEDOM EV trial.

The FREEDOM EV study included an exploratory endpoint of risk assessment, using the French risk assessment tool (11). The authors confirmed the hypothesis that this risk assessment tool would demonstrate greater improvement in the oral TRE group than the control group. A similar finding was replicated using the REVEAL 2.0 risk assessment tool. Also of interest, applying these risk assessment tools to patients at entry into the trial demonstrated that there was not an equivalence of treated and placebo patients. Despite appropriate randomization, patients randomly assigned to treatment had a higher risk profile. These observations support the idea that risk assessment tools can be considered as study endpoints in future trials, and might even be a better randomization tool than our current methods.

An intriguing finding of the study is that mortality was less at study closure (October 2018) in patients treated with oral TRE than in placebo controls (11% vs. 17.4%, respectively; $P = 0.026$). However, this finding is difficult to interpret (and should not be overinterpreted) because mortality was equivalent in both groups at the end of the placebo-controlled aspect of the study. After that point, vital status was not ascertained in 74 (11%) patients, and other important (and contributing) factors such as medication use, medication changes, and development of other comorbid events were not recorded.

Adverse effects were as expected for a prostacyclin agonist, with headache and gastrointestinal complaints most common, occurring in 70% and 40–50% of patients, respectively, which is about twice that observed in the placebo group. Adverse effects contributed to a marked excess in discontinuations in the oral TRE group (19%) compared with the placebo group (4%). This raises the issue of whether this imbalance in discontinuations could influence the results of an event-driven trial design by disproportionately reducing the number of subjects at risk for an event in the intervention group.

The FREEDOM EV trial strengthens evidence to support long-term use of oral TRE for PAH as an add-on with single (but not dual) background therapy. Unfortunately, we have not yet achieved the holy grail of prostanoid therapy: a noninfusion route of administration that offers the efficacy of infusion therapies without the risks and encumbrances. The oral and inhaled routes of administration have advantages, but are simply not as efficacious as infusion therapies.

They have not been tested in the sickest patients with PAH, and their adverse effect profiles and frequency of administration (for inhaled) make it challenging to dose adequately and lead to relatively high discontinuation rates. More study is needed to better understand absorption and metabolism of oral prostanoid agents and develop alternative approaches such as the implantable systemic pump and more convenient and effective inhaled therapies. This and other event-driven trials indicate that we are gaining ground, but still have plenty left to travel. ■

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