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Applying clinical outcome variables to appropriate aerosolized antibiotics for the treatment of patients with cystic fibrosis

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Monotherapy;
Refractoriness;
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Intermittent inhaled antibiotic therapy

Summary
Commercial availability of more than one inhaled antibiotic for the management of chronic *Pseudomonas aeruginosa* lung infections in persons with cystic fibrosis creates a welcome question: Can different inhaled therapies be combined to improve patient outcomes? Although clinicians intuit that antibiotic alternation might extend the duration of benefit, prospective clinical trials will be unable to test this hypothesis. Rather, endpoints acceptable for demonstrating the efficacy of a chronic pulmonary therapy (lung function improvement/stabilization, reduction in exacerbation risk, improvement in quality of life) can test only whether the benefit *amplitude* is increased during fixed treatment periods. Reduction in pulmonary exacerbation risk appears to be best suited for this task, although lack of consensus on an objective definition of exacerbation independent of the decision to treat is a shortcoming. The broader clinical question of whether a patient has become refractory to a chronic therapy over time would be better addressed with a carefully conducted withdrawal study.

Introduction

We have entered a new era with respect to inhaled antibiotic therapies for the management of chronic *Pseudomonas aeruginosa* cystic fibrosis (CF) lung infections. Members of two different antipseudomonal antibiotic classes – aminoglycosides and monobactams – have now been formulated specifically for inhalation and studied extensively in large, controlled clinical trials.[1–7] The commercial availability of these agents and the potential for future approval of others[8] create a welcome challenge for the treating clinician: how to select the "best" chronic treatment regimen for an individual patient when presented with a variety of options. Complexity of choice is not limited to which inhaled monotherapy might be best for a particular patient,[9,10] but includes the possibility that more than one class of inhaled antibiotic might be used in combination to produce a better effect. How will we leverage our knowledge of clinical outcome variables to evaluate different treatment regimens and identify those that are "optimal" for the treatment of CF pulmonary infections?

In the best of worlds, clinicians would be able to rely on objective evidence from randomized, controlled clinical trials that compare different treatment combinations, in order to choose "superior" regimens. However, even the "simplest" comparisons of different regimens will prove difficult and resource-intensive; it may be unrealistic to assume that comprehensive results from randomized trials will ever be available to support these decisions. Nonetheless, it can be instructive to consider what clinical trial endpoints and designs might be best suited to randomized trials of inhaled antibiotic combinations, and the extent to which trials that utilize these outcomes might help to inform inhaled antibiotic treatment choices in the future.

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Clinical trial designs

For studies of different inhaled antibiotic regimens, it can be assumed that active (as opposed to placebo) comparators will be used and that statistical tests will be of superiority. Investigators will be required to predict a difference in outcome among active treatment groups that, if observed, would be accepted as "clinically meaningful" in order to determine adequate sample sizes to attain acceptable power. Although this seems relatively simple, it is not. In the past, studies have tended to focus on the statistical significance of treatment effects compared with placebo, as opposed to whether thresholds exist that define clinically meaningful differences for a given endpoint, with the notable exception being the Respiratory Domain of the Cystic Fibrosis Questionnaire-Revised.[11] Use of active comparators will likely translate into relatively smaller outcome differences among treatment arms than have been observed for placebo-controlled studies, placing a premium on endpoints with lower variances in order to achieve adequate power and manageable sample sizes. Additionally, these studies will be virtually impossible to blind, since different inhaled antibiotics have identifiable packaging, formulation, and associated delivery devices; extended double-blind, double-dummy studies of multiple inhaled antibiotics would be both extremely costly and very difficult to enroll. The potential for introduction of bias in open-label designs is high, and selection of objective endpoints that are less prone to bias is desirable.

Although a variety of regimens and treatment durations might be studied in a prospective trial, the simplest, most frequently discussed regimen is antibiotic alternation, in which the current 28-day on/off use of an inhaled antibiotic ("A" periods of Fig. 1) is supplemented by treatment with a second inhaled antibiotic during 28-day "off-drug" periods ("B" periods of Fig. 1). Although simple enough to describe, results from a randomized comparison of "standard of care" (in which subjects are treated only during "A" periods of Fig. 1) with antibiotic alternation (where different inhaled antibiotics are administered during "A" and "B" periods of Fig. 1) would raise questions for clinicians. Consider that such a design is both a comparison of monotherapy vs combination therapy and of intermittent vs continuous treatment. Superior efficacy associated with a combination regimen could not be unambiguously attributed either to use of multiple inhaled antibiotics or to continuous (as opposed to intermittent) treatment. Assurance that antibiotic alternation (as opposed to continuous treatment) was responsible for an observed benefit would require two additional comparator groups, each receiving one of the two inhaled antibiotics as continuous monotherapy. Such a four-armed study design would be complex, costly, and unlikely to garner much enthusiasm in the CF community.

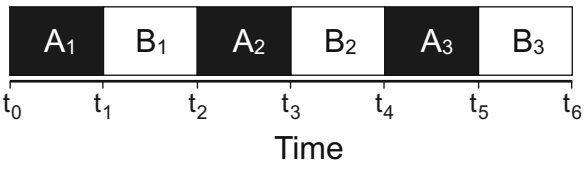

Fig. 1. **Inhaled antibiotic study design template**. Basic chronic-intermittent treatment design used for past inhaled antibiotic studies. Tobramycin inhalation solution (TIS) approval was supported by studies in which subjects were randomized to receive 4 weeks of either active or placebo treatment ("A_n"; gray boxes) interspersed with 4-week rest periods ("B_n"; white boxes).[1] Open-label studies of TIS,[2,10,12,13] aztreonam for inhalation solution (AZLI),[10,14] and tobramycin inhalation powder (TIP)[13] have all used this design, with subjects receiving active treatment during "A" periods of 4 weeks and rest during "B" periods of 4 weeks.

Treatment outcomes

An underlying assumption in the hypothesized superiority of combination inhaled antibiotic therapy over monotherapy is that combining multiple antibiotic classes may delay or slow selection for bacterial opportunists with reduced susceptibility to either antibiotic. In this scenario, infecting bacterial populations would remain relatively more susceptible to antibiotics, and therefore antibiotics should continue to provide benefit for longer periods of time.[15] Although few data are available to support such a hypothesis, it may ultimately prove to be correct over years of cumulative antibiotic exposure. Proponents of this line of reasoning might argue that differences in in vitro antibiotic susceptibilities of bacterial isolates at the end of a randomized study would be a valid surrogate endpoint for efficacy. However, there are several problems with this approach. First, extended studies of intermittent monotherapies suggest that the rate of emergence of bacterial isolates with reduced antibiotic susceptibility is relatively modest over time frames likely to be covered in a prospective study,[10,14-17] leaving little margin for "superiority" (i.e., less emergence of isolates with reduced susceptibilities) associated with combination antibiotic therapy. Perhaps, more importantly, in vitro antibiotic susceptibility has not proven to be predictive of inhaled antibiotic response[9,17] nor has change in bacterial density itself (Fig. 2).[1,9,10,18]

Four endpoints of note have been incorporated into past inhaled antibiotic trials: (1) sustained difference in forced expiratory volume in 1 second (FEV_1)[1,3-6,9,10,13,19,20]; (2) difference in mean rate of FEV_1 decline[2,21]; (3) difference in risk for pulmonary exacerbation[1,2,5]; and (4) difference in patient-reported quality of life (QoL; Table 1).[5,7,10] Each of these outcomes has associated strengths and weaknesses when considered as candidates for a primary clinical trial endpoint.

An advantage of FEV_1 difference as an endpoint is that sample size requirements are relatively smaller than those needed to detect a difference in risk for pulmonary exacerbation. This is particularly true when variance is reduced by measuring age-, height-, sex-adjusted FEV_1 (in liters), rather than FEV_1 % predicted.[22] However, difference in FEV_1 is a cross-sectional measure that may not capture the potential cumulative benefit of more intense treatment resulting from antibiotic alteration. For example, difference in mean FEV_1 at t_6 in Fig. 1 as an endpoint would be unlikely to distinguish between treatment with alternating inhaled antibiotics in each A and B period of Fig. 1, and treatment with the second inhaled antibiotic only in period B_3 of Fig. 1. A more fundamental problem with sustained FEV_1 difference as an endpoint is interpretation of its clinical meaning. The rate at which FEV_1 declines (a different FEV_1 measure) has been proposed as a meaningful predictor of

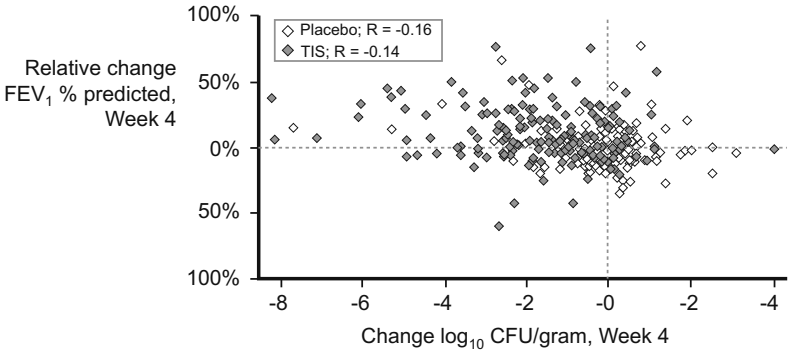

Fig. 2. **Change in *P. aeruginosa* sputum density and pulmonary function at week 4 of the inhaled tobramycin studies.** Subjects receiving tobramycin inhalation solution (closed diamonds) had a lower mean sputum bacterial density and a higher mean pulmonary function than did those receiving placebo (open diamonds) at the end of week 4.[1,18] However, change in bacterial density was a poor predictor of change in pulmonary function in individual subjects. CFU, colony-forming unit; FEV_1, forced expiratory volume in 1 second; TIS, tobramycin inhaled solution.

Table 1
Endpoints used in inhaled antibiotic trials: strengths and weaknesses

Outcome	Requirement		Measure type	Inhaled antibiotic Study precedents
	Sample size	Duration		
FEV_1 difference	+	+	Cross-sectional	1,3-6,9,10,13,19,20
FEV_1 rate of decline	++	++++	Cumulative	2,21
Risk for pulmonary exacerbation	+++	++	Cumulative	1,2,5
Difference in QoL	+	+	Cross-sectional	5,7,10

The relative strength or weakness of each outcome measure as a study endpoint is reflected by the number of + signs. The greater the number of + signs, the greater the relative weakness of the endpoint.

survival,[23,24] but two chronic CF therapies shown to slow lung function decline – high-dose ibuprofen and inhaled corticosteroids – do not produce a sustained improvement in FEV_1.[25-28] Thus, treatments that slow lung function decline do not necessarily produce sustained improvements in FEV_1, and agents that improve FEV_1 may not necessarily slow the rate of FEV_1 decline. Although an argument has been made for the clinical relevance of FEV_1 decline as an endpoint,[23,24] this endpoint requires studies of such extended duration[29] that they would probably be unfeasible. In addition, it is not clear what magnitude of difference in mean decline rate would be accepted as clinically meaningful.

Difference in patient-reported QoL between treatment groups has potential as a study endpoint, although QoL difference is also a cross-sectional measure. Data collected at study completion (t_6 of Fig. 1) would presumably miss any cumulative benefit of more intensive therapy during the study. In order to address this problem, investigators would have to consider averaging QoL across all study visits. The question of whether an improved average QoL is the result of continuous therapy, combination therapy, or both would remain without adequate controls.

The endpoint that may resonate equally with clinicians and regulators is difference in risk for pulmonary exacerbation. Exacerbation risk is a clinically relevant endpoint that has been important for the regulatory approval of inhaled antibiotics in the past, and one that could presumably capture the cumulative effect of more intense antibiotic therapy across a study period. Pulmonary exacerbation risk also lends itself well to pharmacoeconomic analyses, since exacerbations are resource-intensive events.[30,31] However, lack of agreement on an objective definition of exacerbation that does not rely on a clinician's decision to treat is currently a shortcoming of this endpoint.[32]

Arguments have been made for studying treatment-related differences in pathophysiologic markers of CF lung disease, including mucociliary clearance,[33,34] lung clearance index measured by multiple breath washout,[35-37] airway anatomy measured by high-resolution computerized tomography,[38,39] and inflammation in induced sputum.[40,41] However, no data are currently available with which to correlate a treatment-associated difference in any these markers of CF lung pathophysiology with a subsequent clinical response.

Applying study results to clinical care

Randomized trials of inhaled antibiotic combinations are unlikely to exceed 1 year in duration – well short of the duration an individual patient can expect to benefit from inhaled antibiotics. These fixed-duration studies will test for evidence of increased *amplitude* of benefit associated with increased antibiotic intensity. It may be, however, that clinician perception of the potential for benefit of combining inhaled antibiotics is related to longitudinal extension of inhaled antibiotic treatment response rather than to increased benefit within a single year of treatment. For this reason, inability to detect a difference in treatment-associated benefit in a single year may not dissuade clinicians from the belief that inhaled antibiotic rotation will ultimately prove beneficial.

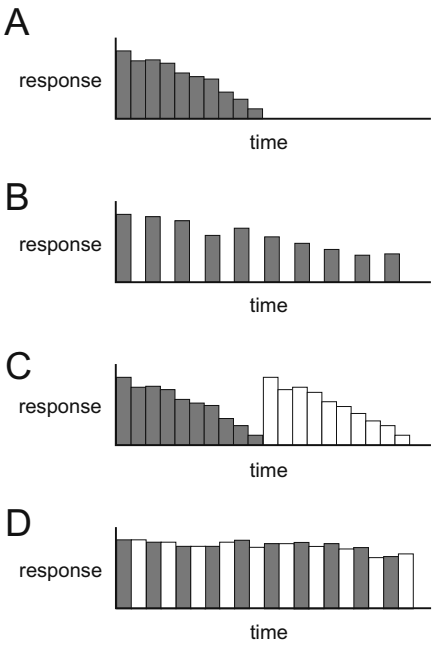

Fig. 3. **Theoretical response profiles for inhaled antibiotics.** Theoretical response (undefined) is plotted on the y-axis for each unit of inhaled antibiotic treatment (x-axis) for a patient. Overall response to an antibiotic can be expressed as total area (response x time). Panel A depicts continuous inhaled antibiotic monotherapy to which a patient becomes refractory during the observation period. Panel B illustrates intermittent inhaled antibiotic monotherapy in which efficacy is retained at the end of the observation period. Overall response (response $\times$ time) in Panel B is greater than that in Panel A. Panel C shows sequential continuous monotherapy with two different inhaled antibiotics, which are represented by gray and white bars. Panel D displays continuous alternating therapy with two different inhaled antibiotics, which are represented by gray and white bars. Total response (response $\times$ time) in Panel D is greater than that in Panel C.

The hypothesis that rotating inhaled antibiotics can increase total patient benefit over a lifetime will likely remain untested until retrospective, comparative effectiveness analyses of patient registry data are conducted years from now. However, assumptions underlying this hypothesis seem logical. For example, it is reasonable to assume that the total benefit an inhaled antibiotic can provide to a given patient is finite and that at some point the patient will become refractory to further antibiotic treatment (i.e., administration of that antibiotic is not associated with any additional benefit; Fig. 3A). It also seems reasonable that the time period over which an inhaled antibiotic retains its effectiveness can be influenced by the dosing regimens used. This is the underlying tenet of intermittent inhaled tobramycin delivery: Continuous inhaled tobramycin treatment for 3 months showed decreasing FEV_1 benefit after the first month of therapy,[18] whereas intermittent inhaled tobramycin treatment provided continued benefit after 6 months[1] and 2 years.[12] Although this construct has never been objectively tested in a single study and these historical studies differ in important ways (e.g., dose, dosing schedule, delivery device, sample size), the concept may nonetheless be true (panels A and B of Fig. 3). If one were to extend this reasoning, a potential benefit of alternating inhaled antibiotic classes would be increasing the net period

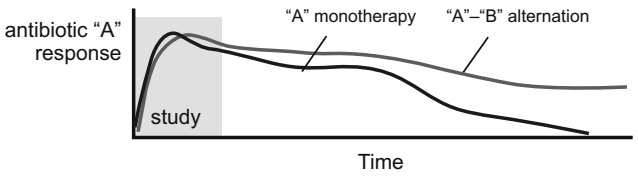

Fig. 4. **Theoretical comparison of response to extended treatment with inhaled antibiotics.** Response (undefined; y-axis) to inhaled antibiotic "A" treatment is plotted over axis time when "A" is administered as a monotherapy (black line) or as part of an alternating inhaled antibiotic regimen. Total benefit can be expressed as the area under the curve (response $\times$ time). The time frame over which alternation of inhaled antibiotics may provide an advantage over monotherapy may be much longer than that covered by a randomized study (gray box) comparing treatment regimens.

of effectiveness for each antibiotic relative to the periods of effectiveness that would be realized if each antibiotic were administered sequentially as monotherapy (panels C and D of Fig. 3). Extension of the effective life of each inhaled antibiotic would presumably play out over the course of years or even decades of a patient's life, and would be unlikely to be captured by the endpoints considered in 6- to 12-month randomized trials (Fig. 4). If the true promise of inhaled antibiotic rotation lies in delaying the time at which a patient becomes refractory to all available inhaled antibiotic therapies, then we have yet to consider a clinical trial endpoint likely to capture that benefit. Shorter-term endpoints may justify or encourage combination antibiotic use by clinicians, but they will not allow us to answer this greater question: Have we increased the effective time span in which we can treat patients?

Testing for refractoriness in patients

If it is true that patients will ultimately become refractory to inhaled antibiotics and that the time course of this phenomenon can be affected by the manipulation of treatment regimens, it follows that clinicians should be seeking evidence that patients have become refractory to inhaled antibiotic regimens they have received for extended time periods. When an individual becomes refractory to a chronic therapy to which he or she had previously responded, treatment cessation should not result in immediate clinical deterioration. Switching a patient from an "old" chronic therapeutic regimen to a "new" regimen (or at least one that has not been used for an extended period) may result in an improvement in clinical status – a circumstance consistent with improved efficacy of the new regimen, but not proof that the prior regimen was no longer effective. Such a conclusion requires withdrawal of therapy and careful evaluation.

It would be impossible to determine if a patient has become refractory to a treatment regimen based on some of the efficacy endpoints discussed above. For example, a clinician could not detect a change in risk for pulmonary exacerbation in an individual subject over a short observation period or whether FEV_1 rate of decline has been influenced by treatment cessation. These cumulative measures do not lend themselves to such short-term assessments. On the other hand, it would be relatively simple to assess an immediate change in either FEV_1 % predicted or patient-reported QoL in an individual following cessation of a chronic therapy. Given that some

uncertainty exists regarding the clinical meaning of modest changes in FEV_1, perhaps change in QoL is the more relevant measure to follow at treatment discontinuation. Carefully conducted withdrawal studies may be the only reliable method for determining that a patient is no longer benefiting from a chronic treatment regimen.

Conclusion

Prospective, randomized studies of the safety and efficacy of combining inhaled antibiotics are feasible. Endpoints that collect data in a cumulative fashion are best suited to detecting superiority in response to a more intensive treatment regimen. These studies will necessarily test the hypothesis that a given intervention provides greater amplitude of benefit (with acceptable safety profiles) over a fixed time period. Although this information will be useful, it may not address the underlying motivations (and the greatest potential benefits) of combining therapies: extension of the effective time during which infections can be suppressed with inhaled antibiotics. It will be the job of care providers to consider whether patients under their care continue to benefit from inhaled antibiotics (alternated or not) after months or years of use. They may wish to consider careful and deliberate N-of-1 "withdrawal studies" to assess refractoriness, and to record these data in a manner that will allow for future characterization of outcomes at the population level using retrospective, observational analyses. Cross-sectional efficacy endpoints may be better suited to this task.

Conflict of interest statement

Donald R. VanDevanter, PhD – Consultant: Baxter International Inc., Genentech, Gilead Sciences, Inc., KaloBios Pharmaceuticals, Inc., Mpex Pharmaceuticals, Inc., Vertex Pharmaceuticals, Inc.

Manfred Ballmann, MD – Consultant: Nordmark Werke; Advisory Committee/Board: Bayer Healthcare AG, Gilead Sciences, Inc., Insmed Inc., Novartis, Vertex Pharmaceuticals, Inc.

Patrick A. Flume, MD – Research Grants: Bayer Healthcare AG, Boehringer Ingelheim Pharmaceuticals, Gilead Sciences, Inc., Inspire Pharmaceuticals, Inc., Mpex Pharmaceuticals, Inc., Novartis, Pharmaxis Limited, Vertex Pharmaceuticals, Inc., Cystic Fibrosis Foundation, National Institutes of Health; Consultant: Gilead Sciences, Inc., Inspire Pharmaceuticals, Inc.; Speakers Bureau: AstraZeneca.

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