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Development of Drugs for Nontuberculous Mycobacterial Disease: Clinicians' Interpretation of a US FDA Workshop

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Abstract

The Food & Drug Administration (FDA) convened a workshop to discuss clinical trial design challenges and considerations related to the treatment of non-tuberculous mycobacterial pulmonary disease (NTM-PD), to include topics such as clinical trial endpoints, duration, and populations. Here the clinicians participating in the meeting provide their interpretation of the discussion, which included FDA and industry representatives. The treatment of NTM-PD typically includes multiple antibiotics for a prolonged period, can be difficult to tolerate, and there is great need for new treatment options. Most individuals have a microbiologic response to therapy, but currently there is a lack of data correlating decreasing bacillary load with patient-reported outcomes or measured functional improvement. Accordingly, trial designs for new therapeutics should incorporate both microbiologic and clinical outcome measures and select appropriate study candidates with capacity for measurable change of such outcome measures. The need for shorter study designs, early primary endpoints, and placebo control arms was highlighted during the workshop

Introduction

The prevalence of pulmonary nontuberculous mycobacterial (NTM) infections has increased considerably in the last decade(1). Published guidelines offer recommendations for diagnosis and treatment(2), but currently there are only two products approved by the United States Food and Drug Administration (FDA) to treat NTM, amikacin liposome inhalation suspension for the treatment of refractory infection due to *Mycobacteria avium complex* (MAC) and macrolides for the treatment of disseminated MAC infection in patients with human immunodeficiency virus. New therapies for NTM pulmonary disease (NTM-PD) are needed to improve clinical outcomes. Achieving this goal will require repurposing existing medications and/or the development of novel drugs. Developing an evidence base for new drugs to meet regulatory requirements necessitates clinical trial designs that can demonstrate efficacy and safety in studies that are feasible and ethical. The FDA convened a workshop in April 2019 to discuss clinical trial design challenges and considerations related to the treatment of NTM-PD, to include topics such as trial endpoints, duration, and populations. In this document, the clinicians participating in the hearing report the challenges and areas of controversy, as well as proposed solutions, highlighted during this meeting. All invited panelists are listed in the Acknowledgements.

Current State of Diagnosis and Treatment of NTM-PD

The reader is referred to other sources for a more complete description of the epidemiology, risk factors, and treatment outcomes in NTM-PD(2). The diagnosis of NTM-PD is based upon clinical symptoms, radiographic findings, and the identification of NTM in cultures of respiratory specimens(2). Signs and symptoms may be pulmonary (e.g. persistent cough, sputum production, hemoptysis) or systemic (e.g. fever, night sweats, weight loss,

fatigue). Radiographic features include nodular or tree-in-bud densities, consolidation, and cavities, frequently in the setting of bronchiectasis or emphysema. Of key importance is that these signs and symptoms are not specific for NTM-PD and it is common that patients experience symptoms for years before a diagnosis of NTM-PD is made(3). Nearly 200 different NTM species have been identified, although many have not been associated with disease in humans. MAC, which includes *M. avium*, *M. intracellulare*, and *M. chimaera* is the most frequently isolated group of NTM pathogens, and causes 80-90% of all NTM-PD in the US, but there are other NTM known to cause disease in humans as well, especially *M. abscessus*(2). Although the principles discussed during this workshop are applicable to other NTM, most of the discussion focused on MAC-PD.

There are published recommendations for the management of NTM-PD(2). When anti-mycobacterial antibiotics are deemed necessary, the treatment generally involves multiple medications administered for a prolonged period. The guidelines recommend treatment with the intent to achieve long-term sputum culture conversion, defined as consistently negative respiratory cultures, implying successful reduction in bacterial burden and, potentially, cure. Accordingly, antibiotic treatment is recommended for a full 12 months after sputum culture conversion. The success of treatment varies based on the specific NTM species being treated, the amount of structural lung disease (e.g. cavities), the antibiotics used to treat the infection, and the ability of the patient to remain on that treatment(2). Best case scenarios have reported culture conversion of greater than 80% for MAC infections, but a recent systematic review and meta-analysis reported a sustained conversion rate of 65% in those who took a three-drug guideline-recommended regimen for a least one year(4), attesting to the need for more effective

therapies. Further, 25-50% or more patients suffer microbiologic recurrence due to relapse or reinfection, generally within three years of stopping antibiotic therapy(5-7).

Monitoring patients for evidence of treatment response or the occurrence of adverse reactions during therapy includes periodic microbiologic assessment, radiologic evaluations, and assessment of patient subjective symptoms and functional status. Clinical experience suggests that most patients experience improvement in their cough and fatigue during therapy(8), and some patients have improvement in other aspects of their symptoms (e.g. improved exercise tolerance, less dyspnea)(9). Although long-term treatment is planned, many patients will experience improvement in their symptoms within the first few months of therapy. Adverse effects of medications can diminish quality of life, and it is not uncommon to stop specific antibiotics within a regimen and/or start new ones if a regimen is not being tolerated(10).

Development of Antibacterial Drugs for NTM: A Patient Perspective

Patient perspectives regarding treatment of NTM-PD have been obtained from a number of sources. An NTM Research Consortium Workshop engaged patients to define research priorities and features of study design(11). The priorities identified with respect to treatment of infection included promoting quality-of-life measures for assessing the effectiveness of treatment and a need to reduce the burden of antibiotic treatment. Prior to this workshop NTM Info & Research, a non-profit US organization advocating for patients with NTM-PD, conducted a survey of patients, of whom 84% had been treated with antibiotics (Table 1). There is wide disparity in the types of symptoms (respiratory vs. systemic) and considerable overlap of symptoms attributed to the infection and the treatment. There was clear interest in the microbiologic endpoint as noted when subjects were asked: “if your treatment could change one thing about your NTM-PD, what would you want that one thing to be?” By a large margin, the

preference was for culture conversion. This likely correlates with the patients' view that the objective of treatment is cure with return of normal health and cessation of medications, and the only path to cessation of medication is associated with culture conversion.

Development of Antibacterial Drugs for NTM: A Regulatory Perspective

The FDA mandate for development of new drugs is the demonstration of sufficient safety and efficacy, the latter defined as improving how a patient feels, functions, and/or survives. Accelerated approval of a drug was recently granted based on sputum culture conversion, but there are limited data evaluating the relationship between this microbiological endpoint and clinical benefits. A review of the literature was conducted to establish whether culture conversion could be used as a surrogate endpoint for clinical benefit. Although there were hints of an association there was no definitive evidence to support surrogacy of the microbiologic endpoint. Retrospective, non-randomized studies suggested higher mortality rates in patients with MAC-PD who remained culture positive despite treatment compared to those who convert to culture negative(12, 13). A retrospective analysis of treatment response in a cohort of nodular/bronchiectatic MAC-PD patients showed both improvement in semi-quantitative sputum culture scores and sputum conversion correlated with symptomatic improvement, especially cough(8). However, studies were from single centers or included a specific subtype of MAC-PD which limits generalizability to the overall population. A primary limitation of using microbiologic endpoints as surrogate for clinical benefit is the lack of prospective randomized control trial data examining this idea. Two studies of treatment refractory MAC-PD suggested that culture conversion correlates with improvements in 6-minute walk (6MW) test, although neither study demonstrated an association between conversion and symptoms or quality of life as measured using questionnaires in the study(9, 14).

These observations do not mean that culture conversion does not correlate with improved clinical outcomes; rather it means only that existing data have not clearly demonstrated that the microbiological outcome can serve as a surrogate marker for clinical benefit as defined by "feels, functions, or survives". The cumulative clinical experience of the expert panelists suggests that sputum culture conversion is a necessary endpoint for the assessment of treatment response and that it does associate with improved symptoms. The lack of data may be due to the orphan nature of the condition, limited "natural history" data on what happens to symptoms of patients that are not treated, overlapping symptoms with underlying lung diseases (e.g. bronchiectasis), and symptoms associated with the treatment itself. The heterogeneity of symptoms in NTM-PD also makes the consistent demonstration of benefit challenging, particularly as currently used instruments to assess patient reported outcomes were not designed for use in patients with NTM-PD. Also, successful treatment does not implicitly mean cure, or eradication of the infection; and it may be necessary to establish a definition of disease control or low disease activity. Regardless, the panel overwhelmingly reiterated that for the treatment of an infectious disease a decrease in the burden of infection (i.e. a decrease in bacillary load as defined by sputum microbiological results) is an essential aspect of decision making for clinical care and is therefore a critical outcome in clinical trials.

Trial Design Considerations

Patient Population Heterogeneity

Previous studies have included heterogeneous subject populations (Table 2), but subjects recruited for a study should have disease manifestations that have the potential to respond to the treatment, that is, disease that is neither so indolent nor far advanced that treatment effects would be difficult to measure. The underlying condition and co-morbidities may be highly relevant in

predicting a response to treatment; patients with CF were excluded from a Phase 3 study(14) based on previous results in which the few CF patients studied did not achieve culture conversion (9). Patients with advanced structural lung disease, especially cavities, are thought to be less likely to achieve culture conversion when compared to those patients with nodules or bronchiectasis without cavities(15). The pathogen and its susceptibility, defined by standard laboratory methods, may also predict responsiveness to treatment. Macrolide resistant MAC is associated with a lower rate of culture conversion(4). Of note, subjects whose MAC showed a high level of amikacin resistance were excluded from studies of amikacin liposome inhalation suspension(14). Finally, the treatment history is highly relevant. Studies have enrolled subjects who met criteria for "treatment refractory" disease (i.e. defined as positive cultures despite $\geq$6 months of a guideline-based multi-drug regimen), but these are different from a population naïve to antibiotic treatment. Even in the treatment-refractory cohorts, there were widely disparate treatment regimens and durations of treatment. Although there are recommendations for drug regimens in MAC-PD, evidence suggests they are infrequently followed in actual clinical practice(16, 17).

Enriching for responders

Subjects enrolled into a trial should have baseline measures of clinical outcomes that suggest they could demonstrate improvement (or worsening), or in other words, they should have the capacity to change. In one study there was a wide range of baseline symptom scores and functional status (as measured by 6MW)(14). Some patients had relatively few symptoms (i.e. normal score) and a 6MW distance in the normal range for healthy subjects, therefore leaving little or no room for symptomatic or functional improvement.

Duration of study

Although treatment guidelines recommend a duration of 12 months following culture conversion, this recommendation does not mean that a drug assessment requires a study of this duration. If a drug is efficacious, a clinical and microbiologic response should be expected within a much shorter period in most instances. Clinicians on the panel suggested strong consideration for limiting trials to 3-6 months or even less, as they desire the opportunity to change treatment if there is a perceived lack of efficacy. Therefore, if a study is to be based upon clinical outcomes then it was felt that the primary endpoint should be assessed earlier than the end of treatment. The observation, described above, that symptoms often improve in the first few months of therapy suggest that symptomatic improvements in short term studies would be demonstrable. This presumes that the outcome measure is not caused by the drug (e.g. cough due to inhaled therapies). Long study durations also increase the likelihood of significant changes to background regimens that will affect assessment of both efficacy and safety of the studied drug.

Comparator and companion drugs

The study of a drug requires comparison to something, whether an active comparator or a placebo, in order to determine safety and efficacy. For the subjects who have treatment-naïve NTM-PD several options could be considered. Monotherapy could be compared to a placebo, but depending on the drug and its mechanism, there may be discomfort using a single drug against NTM for fear of selecting for resistance, although perhaps this fear could be overcome with short study durations. Alternatively, the study drug could be combined with others in order to mitigate potential generation of drug resistance and compared to a placebo regimen. This option perhaps is the most acceptable, as we often do not start patients needing therapy for 3-6 months during initial evaluation in clinical practice, as this time is used to educate patients,

obtain microbiologic information, adopt pulmonary hygiene measures, and assess for disease progression. However, periods of placebo exposure for greater time-periods could be problematic for patient safety, but the allowance of rescue therapy should mitigate such concern. Another option is to use the investigational drug or placebo as an add-on or replacement of a drug in a multi-drug regimen to show "incremental benefit" of the drug. This approach requires a much greater number of patients and much longer study duration to have sufficient statistical power to show a benefit over the comparator regimen (assuming it is an active and efficacious comparator). Lastly, patients with treatment-refractory disease could have the study drug or placebo as an add-on to a failing standard regimen.

This issue raises questions regarding what defines acceptable companion therapy for NTM-PD. All medications have potential adverse effects that may be intolerable or toxic. They may interact with the subject's other medications preventing use of some antibiotics. Therefore, it cannot be presumed that all subjects would be treated with the same medications. Combinations would need to be justified by evidence that supports efficacy, safety, or prevention of resistance.

Study outcome measures

As noted earlier, there is a need for a clinical outcome measure that satisfies regulatory requirements and patient expectations as well. Currently there is no validated instrument for the specific purposes of NTM treatment trials. In order to assess how a patient "feels" the preferred instrument is one that assesses patient-reported outcomes (PRO). A major challenge is the heterogeneity of symptoms reported by patients; for some cough is the primary symptom while for others it may be fatigue, and to include both types of patients in a study the instrument must be sensitive to changes in both. Instruments that have been used in studies include the St.

Georges Respiratory Questionnaire (SGRQ) and the Quality of Life-Bronchiectasis (QOL-B), and each have demonstrated improvement while on treatment(18, 19) although neither has demonstrated obvious differences associated with treatment in controlled clinical trials(9, 14). Neither of these instruments were designed for this purpose, but perhaps they could be refined to be more sensitive to change with respect to NTM-PD, or it may be necessary to develop new instruments. A recent publication evaluating the QOL-B with an NTM module in an observational cohort found improvement to correlate with culture conversion in MAC-PD patients(19). The data suggest potential utility of these PROs and they should be evaluated in prospective fashion. The FDA provides guidance on the development of PROs for use in drug development [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf].

These instruments must also be sensitive to identifying when symptoms are attributed to the underlying condition or the treatment itself. For example, systemic antibiotics could cause fatigue and inhaled antibiotics are known to provoke cough(14). It is difficult to assess when the symptom is both an adverse event and a treatment outcome. This observation raises the necessity for careful consideration regarding the timing of these measurements, whether while on therapy or some time-period after their discontinuation. A limitation of quality of life measures is that they are usually performed at two fixed time points (e.g. baseline and a defined time point during treatment). In the context of NTM-PD, some symptoms may increase while on treatment due to the impact of drugs, but earlier sputum culture conversion could result in a shorter treatment period and, therefore, shorter duration of treatment-related symptoms. Treatment-related symptoms may be mitigated, and the therapy better tolerated, if patients are apprised of

what to expect. Patients typically understand and welcome the concept of "short-term pain for long-term gain"; our current methods of assessment of PROs will need to address this concept as well.

Although PROs are preferred, there are clinician-reported outcomes and performance outcomes that may also be relevant. Radiographic changes have been reported in the literature but there is no validated scoring method that has been tested in NTM-PD treatment trials. Also, radiographic changes do not meet the definition of efficacy in terms of "feels, functions and survives". The 6MW test has been used in studies demonstrating improvement with active treatment in a smaller trial but not in the larger trial(9, 14). Interestingly, however, the measure was significantly correlated with culture conversion in both studies. The 6MW test measures physical functioning but it may not capture the totality of treatment response in NTM-PD; many patients do not experience breathlessness or functional decline. Since the antibiotics would not be expected to directly improve cardiopulmonary performance, the 6MW test might be relevant only for subjects who have demonstrated a significant reduction in infection (e.g. bacterial burden, culture conversion). Finally, it may prove useful to consider composite endpoints, based on a combination of individual endpoints, for drugs that may benefit patients in several ways, as has been used in other chronic inflammatory conditions (e.g. rheumatoid arthritis) that may provide reflections of disease activity that are sensitive to change(20).

Since this is treatment of an infectious disease, there will be continued interest in microbiological endpoints. Successful treatment of NTM-PD by any definition cannot be accomplished without control of the organism in the lung. If microbiological measures could be demonstrated to serve as a surrogate measure, this might allow for shorter studies. The onus is on investigators to demonstrate evidence that supports or refutes the clinical importance of

culture conversion or other microbiological endpoints on relevant clinical outcomes. Studies have primarily used culture conversion as the main interpretation of the antibiotic effect, but other measures may reflect bacterial burden. Semiquantitative culture results have correlated with symptomatic and radiographic improvement, as well as culture conversion(8). Time to positivity in broth cultures can predict microbiologic response to treatment of tuberculosis(21) but this has not been studied in NTM infection. Molecular techniques are increasing available and may provide alternatives to culture based assessment of bacterial burden in the future.

A novel concept would be to demonstrate reduction in bacterial burden that associates with clinical benefits but does not eradicate the pathogen. Since eradication is infrequent given our current therapeutic armamentarium, the notion of suppressive therapy is attractive. Designing trials with suppression of pathogens as a goal may still achieve desired clinical outcomes with long periods of life without disease activity (i.e. remission or low disease activity), as is currently done with inhaled antibiotics for the treatment of chronic *Pseudomonas aeruginosa* infection in CF patients(22). Since many patients with refractory disease remain on antibiotics for years, it would seem that clinicians and patients have already adopted this as an acceptable treatment paradigm.

Monitoring during the study

A key challenge to monitoring during a study is the considerable discomfort expressed by clinicians with blinding to microbiological data during a prolonged study. Blinding to sputum culture results is done to avoid the impact the results may have on clinician decision-making and possibly influencing patient-reported health-related quality of life. In order to maintain equipoise, it is critical for the clinicians to remain blinded, which is another reason why studies

cannot be of long duration. If persistence of NTM in cultures drives treatment decisions, then eventually clinicians will need to know the data if they perceive that patients are not improving.

Conclusions

The clinicians on the panel concluded that NTM-PD is a condition in great need of new treatment options. Considerable knowledge has accrued in the past several years that has clarified the challenges that must be addressed in trial designs. These include selection of appropriate candidate subjects for clinical trials as well as proper outcome measures. There will always be interest in the microbiological endpoints but there is a need to define a clinical outcome measure to be used in NTM treatment trials. We are in agreement that long duration trials (i.e. longer than 3-6 months) are not acceptable, and clinicians expressed a willingness to tolerate trials up to six months with placebo and blinding to microbiologic data, after which they would want to be able to amend the treatment regimen if there is not clear evidence of improvement.

The next step is to validate novel or existing PROs to be used in NTM-PD treatment trials. Such instruments must identify patients whose symptoms could respond to antibiotic therapy and how those symptoms correlate with microbiologic changes. Refinement of PROs will have to occur in prospective observational trials and eventual testing of the PROs in clinical trials. Finally, there could be development of novel functional measures (e.g. wearable devices/steps) that might prove fruitful.

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Table 1: Key findings from surveys of patient with NTM-PD. Results from 465 respondents. Survey conducted by NTMinfo.

Most common symptoms associated with their condition

- Fatigue 77%
- Cough productive of sputum 71%
- Dyspnea 67%
- Coughing without sputum 51%
- Night sweats 49%
- Weight loss 43%
- Hemoptysis 34%
- Lack of appetite 33%
- Chest pain 32%
- Anxiety 32%

Preferences for treatment outcomes

- Improved quality of life 97%
- Increased energy/less fatigue 84%
- Culture conversion 72%
- Reduce coughing 53%
- Improvement in dyspnea 42%
- Repair lung damage 28%
- Improve lung function 27%
- Reduce progression of disease 21%
- Reduce mucus/sputum 20%

Most common reported adverse effects of treatment

- Fatigue
- Dry mouth
- Cough
- Tinnitus
- Decreased appetite
- Dyspnea
- Nausea
- Dysphonia
- Cognitive dysfunction
- Weight loss
- Diarrhea

Table 2. Heterogeneous factors complicating NTM clinical trials

Subject factors

- Underlying disease and co-morbidities
- History of treatment of NTM infection (e.g. naïve, refractory to treatment)
- Radiographic features (e.g. nodules, presence of cavities)
- Pathogen and antimicrobial susceptibility

Clinical endpoints

- Baseline symptoms (i.e. able to detect change?)
- Baseline functional status (e.g. 6MW distance)

Study design parameters

- duration of the study
- superiority vs. non-inferiority statistical analysis
- blinding and monitoring
- companion drugs