

MEETING MINUTES

Subject: Meeting on Paths and Protocol Designs for Developing Improved Treatment for MDR-TB

Date: 10 November 2006

Participants:

- Treatment Action Group (TAG): Mark Harrington, Javid Syed, Bob Huff
- TB Alliance : Ketty Belizaire, Ann Ginsberg, Heather Ignatius, Martino Laurenzi, Nina Schwalbe, Mel Spigelman, Karen Wright, Julia Bakutis
- CDC: Stefan Goldberg, Peter Cigielski, Andy Vernon, Elsa Villarino, Charles Wells (all participating by phone)
- Columbia University (and TBTC): Neil Schluger
- MSF: Martina Casenghi, Tido von Schoen-Angerer, (both participating by phone)
- Harvard Medical School/Partners In Health: Carole Mitnick, Mercedes Becerra (by phone)
- WHO: Matteo Zignol (by phone)
- Albert Einstein College of Medicine: Sarita Shah, Neel Ghandi
- University of Medicine and Dentistry of NJ: Lee B. Reichman
- University of Liverpool: Gerry Davies (by phone)

SUMMARY

Introduction

A. Ginsberg chaired the meeting, which was opened with introductions and a statement of the meeting's purpose: to generate ideas for and discussion of protocol designs and clinical development plans that could lead to timely registration of improved treatments for drug-resistant TB. It was recognized, given the time constraint and the significant number of concept sheets to be presented, that this meeting represented only the beginning of a discussion of approaches and plans for developing improved treatments for drug-resistant TB.

Presentations by a number of participants followed and are summarized below:

1. Mel Spigelman, TB Alliance

M. Spigelman provided a brief overview of the TB Alliance's main approach to improving treatment of MDR-TB: i.e., to discover and develop drugs with novel mechanisms of action for TB, which would therefore be equally effective against drug-susceptible and –resistant TB (and to prioritize compounds with minimal potential for drug-drug interactions, decreasing obstacles to co-administration of multiple drugs and simultaneously maximizing their potential for safe co-administration with ARVs in the HIV-TB co-infected population). One aspect of the TB Alliance's effort to identify optimized, novel drug combinations effective against drug-resistant and –sensitive disease is represented by a recently issued Request for Proposals to systematically perform pre-clinical evaluations of all relevant combinations of new and available compounds with potential in TB treatment.

2, Neil Schluger, Columbia University/TBTC

Neil described two potential designs for phase II trials:

- a. First design based on trial design used in development of HIV drugs for resistant disease; two arm study where groups of patients failing first-line treatment would be allocated to receive category II regimen vs. category II regimen plus novel agent
- b. Second design possible with the availability of required microbiology data: a two arm study consisting of patients allocated to receive optimal background regimen vs. patients allocated to receive optimal background regimen plus novel agent. In TB, it is assumed the optimized background regimen would include a fluoroquinolone (FQ).

Key questions and comments included:

- Consider a primary endpoint based on sputum culture conversion rather than sputum smear conversion
- Before initiating a study of the proposed type one would need significant preclinical and Phase I data on the novel agent(s) (including for example: preclinical safety, efficacy, PK, and toxicology data, and Phase I safety, tolerability, and PK and drug-drug interaction data with the other drugs in the combination to be studied). The lack of applicability of the mouse PK data to human PK will not help with a speedy assessment of these issues.
- One could consider rolling treatment failures from standard treatment in an NTP into a study with the proposed design
- What is the current thinking and what should be the approach to potential monotherapy with a novel agent in the absence of drug susceptibility data in such a trial? Schluger's answer: Ethically, patients without known drug susceptibility results cannot be placed in trial.
- It was noted that any trial for drug resistant disease would require drug sensitivity testing (DST).
- Note: Populations with XDR are diverse and DST is not available in many parts of the world; also, standardized DST methods for many of the SLDs aren't available at all.
- C. Mitnick: Partners In Health (PIH) sees value in conducting a trial to determine which fluoroquinolone is best to use – ie, one of the newer generation vs. older generation FQs (see Mitnick presentation, below)
- One key difference between TB and HIV drug development is that there is a surrogate efficacy endpoint for HIV treatment that can be measured during and at the end of drug treatment that correlates with clinical outcome (i.e., viral load). In TB, the only validated efficacy endpoint requires following patients for at least a year after the end of treatment. It may be difficult to get regulatory authorities to accept sputum conversion as a validated surrogate endpoint for licensure. It was suggested that it might be accepted for provisional licensure, with long-term follow-up commitments for final approval.
- The question was raised as to how dose of the novel agent would be determined for such a trial.
- No drug currently being used for MDR has a specific indication for MDR.

- It was noted that probably none of the novel agents currently being developed for TB has enough toxicology data to support more than 3 or 4 months of treatment.

3. Mark Harrington, TAG

- M. Harrington expressed the opinion, based on experience with HIV drug development, that combination treatment for TB needs to be better and faster and an MDR indication is the channel that could accelerate approval for a new TB drug
- At least two novel, efficacious products are simultaneously needed to treat drug resistant disease, whether MDR or XDR
- Based on the HIV experience, and comments by Leonard Sachs, FDA in 2005, an MDR indication could come faster and the bar for approval might be lower (because reduced safety would be more acceptable in trade for curing previously untreatable TB)
- Study could start in January 2008
- Need EBA data on the novel compounds, key drug interactions (i.e. anti-retrovirals- ARVs), collaboration with industry, individualized DST results
- Proposed study design, based on what was done in HIV trials:
 - Select Optimized Background Regimen (OBR - guided by individual DST)
 - Randomize to new TB Treatment + OBR vs. OBR alone
 - Use standard outcome criteria (sputum/culture conversion at 2 months and/or 4 months): 18-24m follow-up

Based on these considerations, the study design below is proposed:

- Arm 1: A + B+ OBR
- Arm 2: A +C +OBR
- Arm 3: B + C +OBR
- Arm 4: A + B + C + OBR
- Arm 5: OBR

Key questions and comments included:

- It was noted that regulatory authorities would likely not be comfortable with a 2-month endpoint as the basis for registration – it is not a fully validated endpoint and clinical outcome is dependent on the treatment in the ensuing months.
- XDR does not lend itself to randomized clinical trials and it should be dealt with as a compassionate use program; this trial is directed at earlier (MDR) disease.
- The point was raised that provided we had A, B, and C novel drugs and were comfortable with their respective profiles, why not just proceed to a 2-arm study (ABC vs. OBR)? [This design unlike MH's would not distinguish between the contributions of A, B, and C, and therefore might not be approvable.] Since we don't know in TB what each drug even in an OBR contributes, it's not reasonable to insist that we know what each component of a novel regimen contributes. Additionally, at any given time, experimental drugs are usually in different stages of development.

- It was suggested that the proposed design, especially in Arm 4, but in general, would require patients to take an unreasonably large number of drugs, particularly considering concomitant HIV related medications some HIV+ patients are often taking

4. Carole Mitnick, Harvard Medical School/Partners In Health (PIH)

C. Mitnick provided a brief overview of MDR-TB in Peru and on a trial currently being proposed to take place in Peru. This 2-arm trial aims to evaluate the “effectiveness” of ofloxacin vs. gatifloxacin in MDR. The endpoint is sputum culture conversion rate at 4 months. Block randomization is used to stratify the subjects based on treatment failure status. The total number of subjects planned for screening is 700 to yield 600 for randomization and 510 evaluable to have 80% power to detect a difference at 4 months (assuming an increase in conversion rate from 75% to 85% in the intervention vs. control arm).

Also mentioned the possibility of a trial of a salvage regimen. This would examine approaches to treatment in patients not cured by current standard of care, individualized treatment with second-line drugs. There are some promising, if expensive and toxic agents (linezolid, imipenam), which could be combined with a late-generation FQ, and a new agent, to construct an intervention regimen for growing number of patients with no hope for cure with accepted 2nd-line drugs (~20% of patients in Peru). Very preliminary idea that could be refined.

C. Mitnick noted the following changes or additions could be considered in MDR trial design:

- Multi-site implementation
- Change to a factorial design
 - Include treatment with aerosolized capreomycin, or other novel agent
- Explore risks/benefits of binary vs. continuous endpoints

Key questions and comments included:

- Surgery as a treatment modality should/could be included as part of such a trial; however, it was noted that regardless of surgery, treatment with drugs is always required.
- It was imperative that the trial process is kept simple and well-defined and therefore surgery would have no place in such a trial.
- Aerosolized treatment might not be a good approach since TB is often a disseminated disease not limited to the lungs, especially in the settings of high HIV prevalence, for example, many sub-Saharan African countries
 - Some data on newer methods for aerosolized treatment suggest reasonable blood levels may be attainable
 - It is not yet certain if use of aerosolized antibiotics will be effective in treating TB
- If the TB treatment community could be convinced to use routinely in MDR treatment later generation quinolones rather than earlier ones, then the proposed design could be taken off the table.
- What information is available on sites’ capabilities to work on MDR? (It was noted that the TB Alliance’s recent site assessment project did include detailed questions on lab capability, including DST and strain typing, in its

- assessments, but did not focus on readiness for any specific protocol— for drug-sensitive or drug-resistant TB.)
- It was noted that timing of ARVs must be considered in a population with high HIV+ prevalence and could complicate such a trial.
 - C. Mitnick noted that countries that could be considered would include S. Africa, Latvia, and Peru.
 - The question was raised as to who might provide trial insurance for such trials. (This was noted to be the responsibility of the sponsor and there are companies that provide such insurance, although a recent example was provided of a pediatric trial where finding an insurer has been difficult).
 - The question was raised as to who might fund a trial with the proposed design. No clear answer was provided.
 - C. Mitnick noted that Partners In Health has not previously carried out trials and is not experienced in acquiring trial insurance.

5. Gerry Davies, University of Liverpool

G. Davies provided an overview of the barriers to Randomized Controlled Trials in MDR-TB and two conceivable designs (Pontoon, a.k.a. Black Jack, and Snap) which may be applied in studying treatment to MDR-TB (see presentation attached). These designs have similarities to those already discussed (TBTC and Harrington). In general, MDR-TB doesn't seem to have particular advantages for Phase II endpoints based on culture conversion.

However, more "clinical" endpoints with better "validation" and feasible power are available for MDR trials than in PSTB currently so a combined clinical endpoint of treatment failure and/or death might be appropriate for Phase III superiority trials, which would be at least half the size of PSTB equivalence Phase III trials, particularly if the primary endpoint uses survival techniques. The simplest approach would be the Pontoon design but this would not be the most powerful and would also need to ensure that an adequate number of effective drugs were assigned each participant. The Snap design is based on stratification and is much more powerful. It could pose logistical problems but these don't seem any more complicated than similar trials in other areas. In practice, a combination of both approaches (Pontoon and Snap) would be most likely depending on the study setting.

Key questions and comments, included:

- Phase 2 trials in MDR-TB are extremely difficult to conduct due to the lack of homogeneity in the patient population, the need for sophisticated TB labs, etc.
- A potential problem in using such a design model is that the currently proposed definition of endpoints for programs is retrospective and can't easily be applied to prospective trials of this kind. However it was acknowledged that different definitions for use in such trials might be equally appropriate.

6. Mercedes Becerra, Harvard Medical School/Partners In Health (PIH)

M. Becerra proposed a study in treatment of LTBI (using a TBTC protocol - #26, as reference) in which subjects would be randomized to a new drug vs. placebo. The study design would exclude subjects with active disease. This would require a comparison group and likely, a very large sample size. The outcome would be occurrence of disease in subjects treated vs. untreated.

Key questions and comments, included:

- An advantage is that children would be able to be enrolled
- As a ballpark, the sample size would be based on a 50% risk reduction. It is projected that the study would be carried out in 4,000 household (4-5 subjects/household).
- A very large study of LTBI treatment in high HIV+ prevalence communities (CREATE) has been funded by the Gates Foundation

Conclusions and Next Steps

A. Ginsberg closed the meeting by thanking the presenters and all in attendance for an interesting and useful discussion that raised a number of significant issues for MDR-TB clinical trial design and clinical development programs that will require further thought and discussion. M. Spigelman commented that the most important issues moving forward could be seen as falling into 3 categories: study design issues, site capacity and preparation, and funding sources. Next steps were agreed upon as follows:

- Preparation of “high level” minutes from this meeting (TB Alliance will draft and circulate minutes)
- Use the newly created MDR/XDR-TB subcommittee of the Stop TB New Drugs Working Group as a forum for further discussions (Heather Ignatius to follow up with Working Group)
- Maximize opportunities for further discussion on MDR-TB drug development upcoming meetings, including:
 - a. Discuss regulatory/treatment development strategies for MDR-TB with representatives from regulatory agencies at the “2nd Annual Open Forum on Key Issues in TB Drug Development”, being co-sponsored by TAG, the New Drugs Working Group, the Gates Foundation and the TB Alliance, to be held by on 12-13 December 2006 in London, England.
 - b. MSF TB meeting to be held on 11-12 January 2007 in NYC
 - c. WHO/Stop TB Task Force meeting on New Tools for MDR/XDR-TB – tentatively scheduled for Feb. 2007.