RESIST-TB:

Research Excellence to Stop TB Resistance

Research Priorities for New and Existing Drugs in MDR-TB Clinical Trials: A report of the TBTC MDR/XDR-TB Working Group and RESIST-TB

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Areas of MDR-TB Research Interest

A. Current drugs

1. Quinolones. An important area of interest is defining which is the best fluoroquinolone to use in treating MDR-TB, and what is the optimal quinolone dosing strategy. The role of moxifloxacin in MDR-TB treatment is not established; some programs believe it to be superior, but an EBA study suggests it is slightly less potent than high-dose levofloxacin. A PK modeling study suggests that the optimal moxi dose is 800 mg/da, but there are few data on the tolerability of this dose, and none with extended administration. Therefore, a phase 2 study that explored the relative efficacy and tolerability of various doses of levofloxacin and moxifloxacin could yield important information.
    a. If moxi is determined to be superior, and if PR prolongations are an issue with TMC-207 or OPC-67683 (studies are currently underway to assess these possiblities) then it will be important to study PR prolongation when these drugs are used with Moxi (PR prolongations does not occur with levo at doses up to 1500 mg/day).
    b. Despite the usual proscription about use of quinolones in children, both levo and moxi are given to children with TB. Moreover, a PK study of Moxi being given to healthy children who were exposed to MDR-TB is currently underway. Once the results of these studies have been analysed, PK studies of will be needed to determine the doses that achieve optimal PK parameters of flouroquinolones in children with TB.

2. Pyrazinamide. The utility of PZA in persons with genetic PZA resistance is an important area of study, as is the duration of PZA needed to gain maximal benefit. This is felt to be a durable question because PZA appears to potentiate the activity of many of the new drugs, so is likely to remain important for MDR-TB treatment-shortening. However, its utility is unclear when given to patients with genetic resistance. Mouse work indicates that PZA has no benefit for mice infected with M. bovis (which is resistant to PZA due to a His169 → Asp mutation in pncA which abolishes pyrazinamidase activity) but there is no work on the effect of other pncA mutations on response to PZA treatment *in vivo*. At a minimum, mouse studies of isolates with mutations that are commonly seen in

patients are warranted. An observational study of MDR-TB patients in an area where pncA mutations are common would also be of value, since all patients now routinely get PZA, and the effect on two-month culture conversion could be used as an indication of increased bactericidal activity. However, failure to show a difference at 2 months would not rule out a treatment-shortening effect, and followup for failure/relapse would be required for this endpoint.

3. Injectable Agents. The optimal duration of MDR-TB treatment with injectable agents is not known, and these agents are associated with substantial toxicity. Most clinicians believe that they are important for achieving culture conversion in current regimens, although their role in regimens with new drugs may be limited. They may still have an important role in preventing the emergence of resistance to new drugs when these come into general use. Thus, it would be valuable to know if they can be discontinued soon after culture conversion without increasing rates of failure/relapse and emergence of resistance.

B. New Drugs

1. MDR-TB treatment trial. A treatment trial to define the best way to use one or two new agents in the treatment of MDR-TB should be a high priority. Study questions would include identification of the best companion drugs and identification of the shortest treatment duration compatible with an acceptable relapse rate. Outcomes would be relapse and the emergence of resistance to any study agent.
    a. The first step should be a formal assessment of the TBTC's site capacity for such a study, since partnering with other sites/consortia would almost certainly be necessary. A second step will be animal studies that can suggest what combinations and durations will be the most likely to lead to low failure-relapse rates.
    b. The next step will be phase two trials to explore possible durations of treatment for phase 3 trials (these two may be combined in an adaptive design). It is expected that the efficacy of new drugs in combination with PZA and or quinolones in phase two trials of MDR-TB will be able to give an indication of the degree of treatment shortening that can be expected. There is much room for improvement between the current 50% of patients with MDR-TB who convert their sputum in two months (leading to cure in 20 months) and the 75-85% of patients with DS-TB who convert in two months (leading to cure in 95+% by 6-9 months).
    c. For the new drugs that are expected to move into TB treatment, PK studies are needed to determine the doses that achieve optimal PK parameters in children. In addition, if and when more than one new drug becomes available for trials in MDR-TB, it will be important to determine

the interactions between the two before moving forward with phase 3 trials.

2. MDR-TB prevention study. An equally high priority will be studies to define optimal chemoprophylaxis for high-risk contacts of person with MDR-TB. Such high-risk contacts would include children, HIV-infected persons, and pregnant women. An important first step should be assessment of the rates of disease occurring among such high-risk contacts; several such studies are currently underway or have recently been completed but not yet published. Once these data are available, and the PK parameters and necessary drug-interaction studies in children, HIV-infected persons and pregnant women have been completed, a contact study will be a high priority. This study will have a large sample size and require collaboration with other clinical trials consortia. Planning for the necessary PK studies and defining potential collaborations should begin soon.

C. Other study Areas

1. New Diagnostics. TBTC should consider a study to evaluate the effect of new diagnostics (e.g., DNA-based MDR-TB tests) on access to treatment, completion and cure of patients with MDR-TB.

2. Surrogate Endpoints. MDR-TB provides an excellent opportunity to validate surrogate endpoints for TB therapy, since failures are much more common among patients with MDR-TB, and thus sample sizes can be much smaller.

D. Prioritization and strategy

The overall feeling of the working group is that it will be important to study both currently available and new drugs, as the current drugs will continue to have important roles in many areas due to varied patterns of drug resistance. However, since new drugs are likely to become available in the next 2-3 years, it will be important to devise studies of existing drugs that are of one of the two following types: 1) studies of short duration that can yield information in a short period of time; and 2) studies that are observational in nature or that can be adapted to include new agents when these become available. Such studies will therefore be able to avoid being invalidated by the advent of new agents.

With regard to the existing agents, the quinolone question would appear to be the most amenable to a brief, focused study to better define optimization of use, and this question was identified as the highest current priority. The PZA question could be examined as an observational cohort study in areas where PZA resistance is on the order of 50%, and all patients routinely receive PZA. Such a study might able be able to be accomplished with two-month culture conversion as the outcome in a brief, focused

protocol. The injectable question would need longer follow-up, since the outcomes of interest are failure/relapse and emergence of resistance. Such a study might need to be designed so that a new drug could be added to OBT without invalidating the study question.

There was great enthusiasm for studying new drugs when they become available, both for MDR-TB disease treatment and for prevention of MDR-TB in high-risk contacts of MDR-TB. However, it is also clear that a substantial amount of work will need to be done to prepare for such studies. Thus, we grouped the pre-studies and the eventual desired studies under the two rubrics, "treatment" and "prevention". In the "treatment" section, we anticipated that one new drug would come first, followed by a second, but it is certainly possible that both would become available at around the same time, and this possibility needs to also be prepared for.

Lastly, the group recognized that patients with MDR-TB, because of the high rates of failure of current regimens, provide an excellent opportunity for examining new diagnostics and surrogate endpoints. However, the working group does not advocate stand-alone studies of either of these areas in patients with MDR-TB. Rather, all studies of patients with MDR-TB should include these as sub-studies or secondary endpoints.