TB ELIMINATION: DREAM OR REALITY?

29 May – 1 June 2013 – Dubrovnik, Croatia

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Aims:
TB drugs are nowhere a priority. This is for several reasons. They are not profitable. The market is small, mainly poorer countries with lack of ability to pay for the drugs.
There are several instances when companies tried to introduce TB drugs but problems with stakeholders, merger partners and development partners took hold.
In 2000, The Global Alliance for TB Drug Development was started at a conference on new drugs in Capetown, South Africa.
This product development partnership, with major funding from The Bill and Melinda Gates Foundation and others already have agreements with drug manufacturers and has developed the innovative Critical Path Initiative to significantly accelerate development and approval of regimens rather than individual drugs.
The TB pipeline is no longer barren but certainly a far cry from the more robust AIDS drug pipeline.
In the past six months, one drug, Bedaquiline (Sirturo®) from Janssen Laboratories was approved by US FDA. It is significantly more effective than the control, background regimen. The world awaits potential approval of Delamanid from Otsuka which is said to be nearing approval on the European new drug approval entity.

References:
TB ELIMINATION: DREAM OR REALITY?

TRANSFORMING TB TREATMENT
TB Alliance and New TB Drugs on the Horizon
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Dubrovnik, Croatia
May 30, 2013

Faculty disclosure

- Consultant: Cellestis/Qiagen

AIMS

- Aim 1: To recognize the causes of the dearth of new drugs in the pipeline
- Aim 2: To understand the TB drug pipeline, the critical path initiative, and the role and accomplishments of the Global Alliance for TB Drug Development (TB Alliance)
- Aim 3: To understand the role of the only new TB drug in 40 years (Bedaquiline-Sirturo®)
INTRODUCTION

• TB drugs are nowhere a priority. This is for several reasons. They are not profitable. The market is small, mainly poorer countries with lack of ability to pay for the drugs.
• There are several instances when companies tried to introduce TB drugs but problems with stakeholders, merger partners and development partners took hold.
• In 2000, The Global Alliance for TB Drug Development was started at a conference on new drugs in Cape Town, South Africa.
• This product development partnership, with major funding from The Bill and Melinda Gates Foundation and others already have agreements with drug manufacturers and has developed the innovative Critical Path Initiative to significantly accelerate development and approval of regimens rather than individual drugs.
• The TB pipeline is no longer barren but certainly a far cry from the more robust AIDS drug pipeline.
• In the past six months, one drug, Bedaquiline (Sirturo®) from Janssen Laboratories was approved by US FDA. It is significantly more effective than the control, background regimen. The world awaits potential approval of Delamanid from Otsuka which is said to be nearing approval on the European new drug approval entity.

WHY DO WE NEED NEW DRUGS TO TREAT TB?

• Shorter overall treatment duration
• Lower relapse rates
• Development of regimens with fewer adverse effects, particularly less hepatotoxicity
• Development of regimens that can be given easily and safely in combination with antiretroviral therapy
• Development of regimens that are effective in treating MDR-TB/XDR-TB

TUBERCULOSIS DRUG DISCOVERY/DEVELOPMENT AND ITS IMPACT ON TREATMENT

- Streptomycin
- PAS
- Isoniazid
- Pyrazinamide
- Ethionamide
- Kanamycin/amikacin
- Capreomycin
- Rifampin
- Cycloserine
- EMB
THE EVOLUTION OF TREATMENT FOR ACTIVE TB

250 regimens tested in 25,000 patients in order to determine optimal:
- drug combinations
- doses
- dosing intervals
- treatment duration

THE EVOLUTION OF TREATMENT FOR ACTIVE TB

Drugs in clinical development:
- Heart Disease and Stroke: 299
- COPD: 54
- Antibacterials and Antivirals: 89
- Cancer: > 900 (includes vaccines)
  - Lung Cancer: 121
  - Breast Cancer: 111
- HIV/AIDS: 70
- Diabetes: 221
- Anti-tuberculosis: 5.8
- Anti-malarials: 6

Leading causes of global mortality:
1. Ischemic heart disease
2. Stroke
3. COPD
4. Lower respiratory infection
5. Lung cancer
6. HIV/AIDS
7. Diarrhea
8. Road traffic accidents
9. Diabetes
10. Tuberculosis
11. Malaria

TB ALLIANCE VISION

Current

New Treatments in Development

Our Vision

6-30 Months

2-4 Months

7-10 Days
CURRENT TB THERAPY

- **Old**
  - An older drug developed mostly in 1966

- **Long**
  - TB treatment usually takes 6-20 months

- **Complex**
  - Long pill regimens must be taken daily; drug-resistant treatment includes daily injections

- **Expensive**
  - Drug-resistant TB treatment can cost > $10,000

- **Inadequate**
  - Long & complex; breeds resistance & default; incompatible with some HIV treatments; multi-drug resistance often fails

CURRENT THERAPY AND UNMET NEEDS

TB Alliance programs seek to help all TB patient populations

<table>
<thead>
<tr>
<th>Drug Sensitive TB</th>
<th>MDR/TB</th>
<th>TB/HIV co-infection</th>
<th>Latent TB infection</th>
<th>Pediatric TB</th>
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</thead>
<tbody>
<tr>
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<td>Drug need</td>
<td>Drug need</td>
<td>6 month</td>
<td>6 month</td>
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<td>treatment</td>
<td>treatment</td>
<td>medication</td>
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<td>Non-adherence</td>
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<td>3 months</td>
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<td>Resources needed</td>
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</table>

TB ALLIANCE IS A NOT-FOR-PROFIT ORGANIZATION DEDICATED TO THE DISCOVERY AND DEVELOPMENT OF BETTER, FASTER, AFFORDABLE TUBERCULOSIS DRUGS THAT ARE AVAILABLE TO THOSE WHO NEED THEM
COllaborative Model Built to Drive Impact

Each dollar donated leverages $1.60 or more worth of partner services

- A not-for-profit Product Development Partnership, we collaborate with public & private partners to advance TB drug R&D and access
  - PDPs are a proven model to drive research for neglected diseases
  - PDPs are more effective than either public or private sector entities acting alone
- We leverage our partners, making funding go further
- “AAA” Mandate: Any beneficial TB regimens will be adopted, available, and affordable

Evolving landscape

Promising first steps

- First wave of TB drugs have obtained or are nearing regulatory approval
  - Bedaquiline
  - Delamanid
- Important first step: Drugs show potential to improve individual treatment
- Need to transform treatment: Bedaquiline and delamanid are/will be approved on top of the existing MDR-TB background regimen, more needs to be done to broaden those who can benefit from treatment and address key access issues

Percent of Patients Whose Cultures Are TB-Negative After 24 Weeks in Phase II (Study C200)

TAO: An Activists’ Guide to Bedaquiline
REMox TB trial – top line results expected end of 2013
- Successful results would enable registration of 4-month moxifloxacin-containing regimen for drug-sensitive TB; first treatment shortening in nearly 50 years

NC-002 trial – top line results expected Q4 2013
- Results of first trial to treat TB and some MDR-TB patients with identical 4-month treatment. Successful results would lead to Phase 3 registration trial of PaMZ regimen

NC-003 trial – top line results expected Q4 2013
- First trial of second-generation combination regimens. Potential to further shorten TB/MDR-TB treatment to 2 months

MOMENTUM IN TB DRUG RESEARCH
Results of 3 landmark trials expected in the next year
Enrollment completed in January 2012; registration expected in 2014

- Evaluating if a 4-month moxifloxacin-based regimen can perform as well as the current 6-month standard of care in drug-sensitive TB patients.
- Conducted in partnership with Bayer Healthcare, it has the potential to:
  - First new drug to treat drug-sensitive TB in nearly 50 years
  - Shorten treatment by 33%
  - Higher cure rates and less emergence of MDR-TB
  - Reduce cost and burden to healthcare systems and patients

Results expected in 2014

Economic Impact of Shorter Regimens on Patients

Study conducted in Tanzania and Bangladesh

<table>
<thead>
<tr>
<th></th>
<th>Tanzania</th>
<th>Bangladesh</th>
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<tbody>
<tr>
<td>Cost per patient of final two months of treatment</td>
<td>$74</td>
<td>$56</td>
</tr>
<tr>
<td>Cost in final two months as % of average national income</td>
<td>77%</td>
<td>89%</td>
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- Patient costs are significant in the last 2 months
- Particularly high costs from lost work and food supplements

Shortening treatment by 2 months has significant impact

Novel Regimens

Next wave of innovation is underway
- Multi-drug combinations prevent the development of resistance
- Today’s pipeline of TB drugs can be tested together, reducing R&D from decades to years
- TB Alliance brings companies together to allow co-development of drugs
Enrollment of NC-002 is completed; results expected in Q4 2013

**NOVEL REGIMENS IN DEVELOPMENT - PAMZ**

**Moxifloxacin is cornerstone of most advanced novel regimen in global pipeline**

PaMZ is being investigated in both DS- and some MDR-TB patients in the 8-week study NC-002. It successfully completed a two-week clinical study (NC-001) in 2011.

**Results:**
- PaMZ compares favorably to the standard of care
- Shows potential to treat both drug-sensitive and some forms of drug-resistant TB in 4 months with a single combination treatment
- Expected to reduce cost of MDR-TB treatment by 90%
- Simple, affordable therapy could enable the global scale-up of MDR-TB treatment

Enrollment of NC-002 is completed; results expected in Q4 2013

**NOVEL REGIMENS IN DEVELOPMENT – NC-003 TRIAL**

Next generation regimens in the clinic

**NC-003:** Multiple-arm trial testing new regimens

- NC-003 is a multiple-arm study testing additional new TB regimens with the potential to even further shorten treatment for TB and MDR-TB
  - Potential for 2 month therapy
  - 2-week EBA trial
  - Trial includes multiple combinations consisting of bedaquiline, PA-824, pyrazinamide, and clofazamine
  - Currently enrolling patients; top-line results expected Q4 2013

Results expected in Q4 2013

**NIX-TB: “RESCUE” STUDY FOR XDR-TB**

New Chemical Entities in XDR-TB

- There is little/no treatment for XDR/TDR-TB
- Several new drugs with no pre-existing resistance could have promising data by 2014
  - Bedaquiline, delamanid, PA-824, sutezolid, SQ109
- Proposal: initiate global study of combinations of NCEs in patients with XDR/TDR-TB at select centers with aim of cure
  - Potential collaborators: Janssen, Otsuka, TB Alliance, Pfizer, Sequella
  - Help patients who would otherwise die
  - Combines a “compassionate use” program with a clinical trial to advance understanding of entirely novel regimens, which can then be applied in DS- and MDR-TB
PEDIATRIC TB

TB is a leading killer of children, yet appropriate pediatric regimens don’t exist

- No products meet the revised WHO dosing recommendations for childhood TB medicines, leading to drug resistance & poor outcomes
- Key challenges to overcome:
  - Understand the size of the problem
  - Incentivize manufacturers to develop childhood formulations for current first-line drugs
  - Work with regulatory authorities to develop pediatric dosing guidelines and speed regulatory process
  - Work with countries to prepare for new pediatric drugs
  - Create reservoir of knowledge to accelerate introduction of new pediatric drugs
- Goal: First-line drugs in the correct childhood dose

PROFILE OF NEW TB REGIMENS

New treatments will help achieve a future free of TB!

FUNDING NEED

TB R&D is gravely under-funded

- 67% funding gap in TB drug R&D investment vs. WHO recommended targets to reach TB control goals
- Results from 3 clinical studies expected in 2013; success means more funding needed for late stage trials
- TB Alliance Phase 3 trials cost approximately $75M. Advanced Phase 2 trials cost between $8-10M and earlier stage Phase 2 trials roughly $2M

Promising regimens need funding to take them through the final stages of testing and to people who need them
Conclusion

- MDR-TB and XDR-TB are caused by humans, they don’t exist in nature. The most common causes are inappropriate treatment by the practitioner and lack of patient adherence.
- That said, we desperately need newer shorter regimens. The most effective of which will be combination of new molecules.
- The critical path initiative of testing several drugs in combination rather than sequentially is an effective approach.
- New drugs need to be used carefully to preserve their sensitivity and effectiveness.

INFORMATION LINE
1-800-4TB-DOCS (482-3627)
www.umdnj.edu/globaltb