Old Drug/New Formulation for Europe: Minocycline

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Disclosure

• Employee and Shareholder of The Medicines Company
Topics

- Regulatory history
- Data
- Clinical Program for Europe
- Public-Private funding
  - Antibiotic Resistance Leadership Group (ARLG)
  - Innovative Medicines Initiative (IMI)

MINOCIN® (minocycline for Injection)
Focus on MDR Acinetobacter

Regulatory Overview
- Minocycline in oral and IV forms originally approved in the US and ROW in the 1970s - history of extensive use of oral form for treatment of skin infections
- IV form withdrawn from US market in 1990s due to non-use; restored upon request of US government
- Minocin® IV is one of the few FDA-approved antimicrobials for the treatment of infections caused by Acinetobacter spp.
- sNDA for new formulation approved in US in April 2015
- QIDP designation by US FDA for HABP/VABP, other resistant gram-negative pathogens in CF

Data Highlights
- Ongoing surveillance studies in the US and worldwide show minocycline is one the most active antibiotics against MDR Acinetobacter species
- Microbiological studies show clear differences in resistance mechanisms compared to other tetracyclines, including tigecycline
- Synergy with other antimicrobials (e.g., polymyxins, carbapenems)
- Nephroprotectant when given with colistin
- New nonclinical and clinical studies planned, including registration program for EU
Focus on *Acinetobacter*

**CDC Antibiotic Resistant Threats in the United States**

2% of all HAI are due to *A. baumannii* (7% in ICUs)

Striking increase in imipenem-resistant *Acinetobacter* infections in the U.S.

Imipenem-resistant *Acinetobacter* represented ~5% of *Acinetobacter* infections in 2000.\(^1\)

<table>
<thead>
<tr>
<th>Year</th>
<th>U.S. National</th>
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<tbody>
<tr>
<td>2000</td>
<td>7.67%</td>
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<tr>
<td>2010</td>
<td>40.76%</td>
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</tbody>
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Carbapenem resistance is a common component of *Acinetobacter* multidrug resistance.\(^2\)


Percentage of MDR *Acinetobacter* spp. By Country in Europe

The Medicines Company Confidential and Proprietary

CONFIDENTIAL
Minocycline: In Vitro Activity is Preserved in MDR Isolates

Susceptibility (CLSI or FDA Breakpoints) of Clinical Isolates of Acinetobacter sp. (2011-2012; TEST program)
(Hawser et. al., ICAAC 2013, Poster C2-1625)

Minocycline Activity Against *Acinetobacter baumannii* complex isolates in 2013

**Table 1**
Summary of minocycline activity tested against selected Gram-negative bacteria isolates from Global surveillance (2013).

<table>
<thead>
<tr>
<th>Organism (no. of isolates)</th>
<th>MICs (mg L⁻¹)</th>
<th>0.015</th>
<th>0.03</th>
<th>0.06</th>
<th>0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>MBC</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter baumannii</em> complex (1,312)</td>
<td>6 (65) 40 (35) 100 (111) 199 (19.4) 126 (200) 160 (41.2) 109 (86.5) 120 (58.7)</td>
<td>2</td>
<td>8</td>
<td>178 (72.3) 199 (87.4)</td>
<td>165 (1060) 2</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>MDR (1070)</td>
<td>1 (92) 4 (05) 14 (18) 30 (44) 96 (13.7) 155 (282) 100 (36.4) 191 (49.3)</td>
<td>2</td>
<td>8</td>
<td>178 (162) 197 (84.6)</td>
<td>165 (1060) 4</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>--</td>
<td>--</td>
<td>8 (83) 12 (2.3) 68 (9.3) 130 (21.1) 100 (33.7) 105 (44.0)</td>
<td>170 (162) 191 (83.1)</td>
<td>165 (1060) 4</td>
<td>8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em> (30)</td>
<td>--</td>
<td>1 (02)</td>
<td>4 (1.1) 67 (15.5) 161 (902) 116 (75.2) 64 (86.0) 36 (96.8)</td>
<td>11 (90.1) 3 (98.8)</td>
<td>1 (1000) 0.25 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Flamm et al; DMID 85, 2016, 352-355
Unlike Tigecycline, Minocycline Does Not Select for Clinically Significant Resistance in Acinetobacter (Lomovskaya et. al. ICAAC 2013)

- Tigecycline but not minocycline can select for single-step mutants with clinically relevant resistance
  - Higher level resistance to multiple antibiotics observed
    - Tigecycline, azithromycin, aminoglycosides: 8 to 16-fold, likely due to over-expression of AdeABC pump (associated with tigecycline failures in patients)
  - No selection of resistance with minocycline
  - Minocycline is not a substrate for the AdeABC efflux pump

PK-PD Implications in Humans
- Minocycline plasma Cmax (3-8 ug/ml) and trough levels obtained with FDA approved dosages is above mutant prevention concentration of minocycline (1 ug/ml) in this experiment
- In contrast, plasma Cmax (< 1 ug/ml) for tigecycline at FDA-approved doses is within mutant selection range

Minocycline and Polymyxin B Efficacy Alone or in Combination vs. Acinetobacter Pulmonary Infection in Mice (Bowers et. al., AAC 2015)

Pulmonary infection in neutropenic mice
Minocycline, Polymyxin B MICs 1 and 2 mg/L
Humanized dosing of minocycline “100 mg BID”
Results
- Minocycline or Polymyxin B improved survival alone or in combination
Minocycline when Given with Polymyxins May Be Nephroprotectant

- Retrospective analysis of 5025 patients in the Premier Database that received colistin and 95 who received colistin and minocycline

<table>
<thead>
<tr>
<th></th>
<th>COL</th>
<th>COL-MIN</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted Outcomes</td>
<td>n=5025</td>
<td>n=95</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ARF</td>
<td>23.0%</td>
<td>11.6%</td>
<td>0.438 (0.233, 0.825)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>29.9%</td>
<td>31.6%</td>
<td>1.085 (0.701, 1.679)</td>
<td>0.725</td>
<td></td>
</tr>
<tr>
<td>30-day readmission</td>
<td>27.0%</td>
<td>30.8%</td>
<td>1.205 (0.708, 2.051)</td>
<td>0.421</td>
<td></td>
</tr>
<tr>
<td>PSM (1:8 matching)</td>
<td>n=688</td>
<td>n=86</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ARF</td>
<td>24.7%</td>
<td>11.6%</td>
<td>0.401 (0.203, 0.793)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>32.0%</td>
<td>32.6%</td>
<td>1.027 (0.636, 1.657)</td>
<td>0.913</td>
<td></td>
</tr>
<tr>
<td>30-day readmission</td>
<td>28.0%</td>
<td>29.3%</td>
<td>1.067 (0.585, 1.944)</td>
<td>0.333</td>
<td></td>
</tr>
<tr>
<td>Logistic regression model</td>
<td>n=5,025</td>
<td>n=95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARF</td>
<td>0.390 (0.202, 0.753)</td>
<td>0.005</td>
<td>0.681</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.113 (0.548, 1.947)</td>
<td>0.699</td>
<td>0.711</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day readmission</td>
<td>1.12 (0.346, 3.915)</td>
<td>0.702</td>
<td>0.598</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lodise et al, Poster, ECCMID 2017

Pharmacodynamics of Minocycline In a Rat Pneumonia Model
Pooled Results for 6 isolates with 100-fold range in MICs

Emax = 5.42
EC50 = 19.66
Gamma = 2.07
R2 = 0.86

Change in Log CFU/mL as Compared to Untreated Groups at Start of Treatment

Free 24hr AUC/MIC
**Pharmacodynamics of Minocycline**

**Mouse Pneumonia Results – Summary and Conclusions**

<table>
<thead>
<tr>
<th>Strain</th>
<th>Minocycline MIC (mg/L)</th>
<th>Free 24h AUC/MIC for Static Effect</th>
<th>Free 24h AUC/MIC for 1-log of Bacterial Killing</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB1016</td>
<td>0.25</td>
<td>10.61</td>
<td>24.22</td>
</tr>
<tr>
<td>AB1161</td>
<td>1</td>
<td>16.07</td>
<td>18.82</td>
</tr>
<tr>
<td>AB1157</td>
<td>2</td>
<td>13.66</td>
<td>17.31</td>
</tr>
<tr>
<td>AB1129</td>
<td>4</td>
<td>11.25</td>
<td>13.10</td>
</tr>
</tbody>
</table>

- Minocycline produces a bacteriostatic effect with a 24h Free AUC/MIC of 10 – 16 and kills 1-log CFU with a 24h Free AUC/MIC of 13 – 24.
- A 100 mg BID dose of minocycline produces a 24h Free AUC of 40 which would produce a 1-log CFU kill with MICs up to 2 mg/L.
- A 200 mg BID dose of minocycline produces a 24h Free AUC of 80 which would produce a 1-log CFU kill with MICs up to 4 mg/L.
- Current 100 mg – 200 mg BID dosing produces exposures that were found to be bactericidal against strains with MICs up to 4 mg/L in this animal model of infection.

**Overall Plan is to Study Higher Doses of Minocycline in the EU Than Those Currently Approved in the US**

- Plan for development and approval in EU is to study higher doses than those approved in the 1970s in the US.
  - Studies conducted to support development in EU could potentially support a label change in the US.
- Benefits of higher dose:
  - Improve PK-PD
  - Support for higher susceptibility breakpoints → coverage of a greater proportion of isolates of Acinetobacter spp.
Safety of Minocycline at Higher Doses

- Completed preclinical toxicology studies support use of higher doses

- Higher doses of minocycline IV has been studied as a neuroprotectant in post-stroke and spinal cord injury patients

- Casha, et. al. Brain 2012;135:1224-1236
  - Single center, randomized, double-blind, placebo controlled trial in subjects with acute spinal cord injury
  - Placebo (25 subjects), low dose minocycline (200 mg BID) (5 subjects), high dose minocycline (400 mg BID) (22 subjects)
  - No difference in incidence or severity of AEs across the 3 groups

- Fagan, et. al. Stroke 2010;41:2283-2287
  - Multi center, open label trial in subjects with acute stroke
  - 132 subjects across 4 groups: 3, 4.5, 6 and 10 mg/kg given as a single loading dose, then half the loading dose BID. 99 subjects enrolled in the 10 mg/kg group with the max. dose being 700 mg as a loading dose, then 350 mg BID
  - Most common AEs were headache and N/V, both seen in approx. 9% of subjects
  - No evidence of a dose response for AEs

Clinical Development Plan and Funding via Public Private Partnerships
Minocin Clinical Trial Development Program

**ARLG: Phase 1 Study in US:**
- Single Dose PK study in ICU patients

**Combacte-Net: Phase 1 Studies in EU:**
- PK and Safety study of single and multiple ascending doses in normal subjects
- PK and safety study in patients with varying degrees of renal impairment
- PK study in lung epithelial lining fluid in normal subjects

**Combacte-Net: Global Phase 3 Study:**
- Efficacy and Safety study in patients with HABP/VABP or bacteremia due to *Acinetobacter baumannii* complex

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**The Medicines Company Infectious Disease Group has Received Exceptionally Strong Support from Government Partnerships**

- Meropenem-vaborbactam development (~$56M to date)
- Collaboration with BARDA, recently expanded into Other Transaction Authority (OTA) agreement that give us potential to receive up to $132 million in funding to support further development of meropenem-vaborbactam and other programs
- EU’s largest public-private partnership supporting development of new drugs
- COMBACTE-NET: Cost share for 4 clinical trials supporting development and registration of Minocin IV in the EU (~10 million euros)
- ARLG clinical pharm study of MINOCIN in ICU patients in US
- Collaboration with Monash University on the discovery of new polymyxins supported by NIAID
- NIAID preclinical testing has supported our discovery programs
ARLG
Antibiotic Resistance Leadership Group

Who is the ARLG?
Antibacterial Resistant Leadership Group
COMBACTE/IMI
Combating Bacterial Resistance in Europe
Innovative Medicines Initiative

Innovative Medicines Initiative (IMI): a new way to collaborate

- The largest public-private partnership in life science R&D

- IMI1 Started in 2008, ended in 2014
  - 11 Calls launched
  - IMI1 COMBACTE projects run until:
    - end of Feb. 2020 (CARE),
    - end of Feb. 2021 (NET),

- IMI2 started in 2015
Innovative Medicines Initiative (IMI): a new way of working

- **Main objectives:**
  - Accelerating the development of safer and more effective medicines for patients in Europe
  - *Boosting* the biopharmaceutical sector in Europe
  - Creating a collaborative environment for academia, industry, SMEs, regulators, patients

- **ND4BB** is part of the *Action plan against the increased threats from AMR* launched by the European Commission in November 2011

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**Overall Architecture of the ND4BB Programme**

**ND4BB cross topic collaboration and dissemination**

- **ENABLE**
  - Discovery & development of new drugs combating Gram-negative infections
- **COMBACTE-NEP**
  - a) Enabling Clinical Collaborations and Refining Clinical Test Design
  - b) Clinical Development of component(s) for Combinations
  - c) Clinical Development of UE4893
- **COMBACTE-CARE**
  - Clinical Development of antithetical agents for Gram-negative antibiotic resistant pathogens
- **COMBACTE-MAGNET**
  - Systemic molecules against HAI's due to clinically challenging Gram-negative pathogens
- **iABC**
  - Inhaled Antibacterials in Cystic fibrosis (CF) and non-CF BE
- **DRIVE-AB**
  - Driving re-investment in R&D and Responsible use of antibiotics

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**ND4BB Information Center**

All data generated is submitted and accessible to all consortium partners
COMBACTE: Combating Bacterial Resistance in Europe

Three consortia:

Create a self-sustaining antibacterial development network
- Expanding research and laboratory networks
- Optimal alignment of clinical trials with investigator sites
- Obtain clinical and epidemiological data

Increase efficiency of antimicrobial drug development
- Align clinical trials with cutting edge molecular methodologies and trial design
- Deliver clinical trials with various candidate compounds from pharmaceutical companies
COMBACTE collaboration

- > 800 hospitals
- 55 academic partners
- 42 countries
- 8 EFPIA partners

COMBACTE FUNDING

Source of COMBACTE’s budget
- €208 million from the EU
- €285 million from the EFPIA
- €11 million from other sources
- €504 million in total

Utilization of COMBACTE’s budget
- €250 million on COMBACTE-NET
- €85 million on COMBACTE-CARE
- €169 million on COMBACTE-MAGNET
- €504 million in total
How Does It Work?

• Description of Work Developed/Funded with detailed timelines/budget
  - IMI/The Medicines Company

• Academic Partners
  - Oliver Cornely: University of Cologne
  - Bruno Francois: University of Limogues
  - Alasdair MacGowan: University of Bristol

• Management Board
• Scientific Committee
• Ethics Committee
• Safety Committee

ECRAID
European Clinical Research Alliance on Infectious Diseases

• Building on COMBACTE and PREPARE: joint pathway to sustainability
• Now is the time: international momentum and Europe’s chance to lead by example
• The concept and added value of ECRAID in a nutshell
• Current status, next steps and request from EFPIA
Summary

- Minocycline is approved in the US for the treatment of Acinetobacter spp.

- Development program at higher doses for registration in EU for the treatment of Acinetobacter baumannii complex infections is underway
  - Funded in part by IMI/COMBACTE

- Minocycline development program will hopefully be a part of building/supporting IMI/COMBACTE to become ECRAID-European Clinical Research Alliance on Infectious Disease