What is the target group for antitoxin treatment to prevent *Clostridioides difficile* infection?

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Transparency declaration

• I am a Consultant advisor to CHAIN Biotechnology
• I co-supervise a BBSRC iCASE DTP PhD-funded student with industrial partner CHAIN Biotechnology
Presentation overview

- Toxins in disease pathogenesis
- Antitoxin strategies
- Role of humoral immunity in host defence
- Evidence review
- Likely place in therapy
- Unanswered questions and future considerations
Structure of \textit{C. difficile} toxins A (TcdA) and B (TcdB)

Aktories K et al 2017 \textit{Annu. Rev. Microbiol} 71; 281-307
Toxin-induced CDI pathogenesis

Aktories K et al 2017 Annu. Rev. Microbiol 71; 281-307
Antitoxin antibody-mediated therapies for C. difficile infection

Passive immunotherapies

• Systemic:
  • Humanised antitoxin mAbs
  • Polyclonal IVIg

• Oral
  • IgAbulin
  • Hyperimmune bovine Ig concentrate
  • Mucomilk (polyclonal-antibody enriched whey protein concentrate)

Active immunotherapies/toxin-based vaccines

• Systemic:
  • PF-06425090 (Pfizer; phase III)
    • Genetically and chemically detoxified TcdA and TcdB
  • VLA84 (Valneva; phase II)
    • Recombinant chimeric protein linking binding domains of TcdA and TcdB
Small molecule inhibitors of toxin domains

*Compounds found to be active against TcdA and TcdB

1983 Detection of antitoxin antibodies in sera of healthy and infected subjects

1984

1986

1988

1990

1991 IVIg for chronic relapsing C. difficile colitis

1992 Systemic and mucosal Ab response to toxin A in patients with CDI

1994 Higher serum IgG anti-toxin A and faecal IgA anti-toxin A in single v relapsing CDI

1995 Selective neutralization of toxin A by IgA

1996

1998

2000 High serum IgG antitoxin A associates with asymptomatic carriage

2001 Low serum IgG antitoxin A associates with higher risk of rCDI

2000

2002

2004

2006

2007 Low IgG2 and IgG3 subclass responses to toxin A in rCDI

2006 IVIg for Rx of severe, refractory rCDI

2007

2008

2010

2012

2014

2016 Detection of isotype specific antitoxin Abs by microarray

2013 Circulating Ab and memory B-cell responses

2015 Detection of serum antitoxin IgG by electrochemiluminescence

2016 Bezlotoxumab

1991 IVIg for chronic relapsing C. difficile colitis

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1995 Selective neutralization of toxin A by IgA

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2006 IVIg for Rx of severe, refractory rCDI

2007 Low IgG2 and IgG3 subclass responses to toxin A in rCDI

2016 Bezlotoxumab
NB: No correlation between binding and neutralising anti-toxin A antibody levels and resolution of symptoms (Johnson S et al 1992 JID 166; 1287-94)

1 = acute; 2 = convalescent; 3 = asymptomatic CD excretors; 4 = healthy controls
Serum IgG antitoxin A levels increase with age in healthy controls; ↑ in men c/w women > 60 yrs

72% adults and 40% children < 2 yrs have detectable IgG to toxin A

Non-immunocompromised patients (grey) ↑ serum and faecal antibody levels than cytostatic-treated patients (black) and controls (white)

Relation of antibody levels to presence of relapse

Symbols: ■, no relapse; ●, relapses; □, control.

Low serum IgG anti-toxin A levels (< 3.00 EU) associate with ↑risk of developing CDI; OR 48; (95% CI, 3.4-678; P <0.001))

Recurrent CDI associates with:
• Low day 3 IgM anti-toxin A; OR 9 (95% CI 1.6-49.4)
• Low serum IgG antitoxin A (<1.29 EU) at day 12; OR 48 (95% CI 3.5-663)

Circulating *C. difficile* toxin A-specific, antigen-activated memory B cells by flow cytometry

Monaghan et al *PLoS One* 2013; 8 (9) e74452

n=16 (39 blood samples collected median 181 (81-415) days after CDI onset)

[0.82 (0-4.93) % vs 0.33 (0-2.12) %]

**Toxin A- and B-specific ASC frequencies in patients with CDI by ELISpot**
Critical evidence review

- Heterogeneity in study populations and methodologies
- Lack of concordance with binding and neutralising titres
- Presence of neutralising antitoxin antibody activity independent of clinical response
- Role of non-neutralising antitoxin antibodies has not been defined
- Longitudinal surveys assessing dynamics of response often missing
- Poor understanding of memory B cell response
- Mucosal immunity often not assessed – reliance on circulating responses
- Phenotypic variation in antibody response often not explored
IVlg therapy for severe *C. difficile* colitis

- IVlg induces clinical resolution in 2 patients with severe PMC not responding to SOC metronidazole and vancomycin
- IgG antitoxin A and B antibodies are readily detected in IVlg preparations
- *C. difficile* toxin neutralising activity evident at IgG concentrations of 0.4-1.6mg/mL

Salcedo *et al* 1997 Gut; 41: 366-370
(a) Immune reactivity of multi-isotype specific antibodies to *C. difficile* toxin and non-toxin antigens in 3 commercial IVIg preparations by protein microarray. Total IgG, IgG1 and IgG2 isotypes give highest binding reactivities against toxin A, toxin B and binary toxin (pCDTb).

(b) IVIg neutralisation efficacy against *C. difficile* native whole toxins A and B.

(a) Antibody reactivities against *C. difficile* antigens in patient sera pre- and post IVIg.

(b) Serum IgG responses to toxins A, B and binary toxin (pCDTb) pre and post-IVIg.

(c) Neutralisation activity against *C. difficile* toxins A and B pre- and post-IVIg.
IVIg – place in therapy

• IDSA/SHEA 2017 guidelines:
  • IVIg can be used at concentration of 150-400 mg/kg, in patients with fulminant CDI not responding to vancomycin and metronidazole
  • Lack of randomised control trials
  • Lack of consensus regarding optimal dosing, timing of administration and type of commercial IVIg

• World Society of Emergency Surgery (WSES) 2019 guidelines
  • IVIg should only be used as adjunct therapy in patients with multiple recurrent or fulminant CDI until results from large RCTs are available

• Public Health England:
  • Severe (or recurrent) CDI is considered an appropriate use of IVIg
Preclinical development and subsequent testing of neutralising fully human monoclonal antibodies directed against *C. difficile* toxins A & B

**2006:** Anti-toxin A HuMAb, *actoxumab* (MK-3415, GS-CDA1, or MDX-066) and anti-toxin B HuMAb, *bezlotoxumab* (MK-6072, MBL-CDB1, or MDX-1388) subsequently taken forward
- Both actoxumab and bezlotoxumab are IgG1 monoclonals and map to putative receptor binding domains of respective toxins.

- Bezlotoxumab binds to 2 separate sites within the N-terminal half of combined repetitive oligopeptide (CROP) domain to toxin B, partially occluding 2 of 4 putative carbohydrate binding pockets for the toxins (Orth P et al 2014 J Biol Chem; 26: 18008-18021).


Toxin-directed HuMAbs protect hamsters

Babcock et al 2006 Infect Immun; 74: 6339-6347

PRMARY CHALLENGE MODEL
CDA1: 50mg/kg/day (4 days)
MDX1388: 10-50 mg/kg/day

RELAPSE MODEL
CDA1: 60mg/kg/day (4 days)
MDX1388: 20 mg/kg/day
Toxin-directed HuMAbs protect mice in *C. difficile* challenge models

- Mouse model of systemic toxin challenge
- Intra-gastric spore challenge model (prophylactic and therapeutic paradigms of primary CDI)
- Mouse model of recurrent *C. difficile* infection

Mechanisms of protection

Prevention of damage and inflammation in gut wall in ileal loop and spore challenge models

Mutant forms of antibodies that do not bind to Fcγ receptors also provide protection, suggesting MOP is direct neutralisation via F(ab’)2 regions and does not involve host effector functions

Normalisation of gut microbiota (reduction in *Enterobacter* and restoration of core components of original microbiota, *Blautia*, *Akkermansia*, and *Lactobacillus*)

Yang Z et al 2015; *Infect Immun*; 83: 822-831
Dzunkova M et al 2016; *Front Cell Infect Microbiol*; 6:119
Phase 2 trials

Subjects randomized in double-blind fashion to IV CDA1/actoxumab (10mg/kg) or placebo while on SOC treatment for CDI

• Results:
  • 29 subjects received actoxumab; 17 subjects placebo
  • CDI recurrence similar in actoxumab and placebo arms (5/29 [17%] and 3/17 [18%]; P = NS) during 56-day follow up
  • Predictors of recurrence
    • Lower neutralising anti-toxin B antibodies at day 14
    • Lower anti-toxin A neutralising antibodies at day 28
    • Infection with epidemic BI/NAP1/027 strain

Leav BA et al 2010 Vaccine; 28: 965-9
Phase 2 trials

Treatment with Monoclonal Antibodies against *Clostridium difficile* Toxins

Israel Lowy, M.D., Ph.D., Deborah C. Molrine, M.D., M.P.H., Brett A. Leav, M.D., Barbra M. Blair, M.D., Roger Baxter, M.D., Dale N. Gerding, M.D., Geoffrey Nichol, M.B., Ch.B., William D. Thomas, Jr., Ph.D., Mark Leney, Ph.D., Susan Sloan, Ph.D., Catherine A. Hay, Ph.D., and Donna M. Ambrosino, M.D.
Phase 2 trial evidence for toxin-directed HuMabs

Randomised, double-blind, placebo-controlled study

- **Active comparator:** HuMabs against *C. difficile* toxins A (CDA1/actoxumab) and B (CDB1/bezlotoxumab) administered as single infusion (10 mg/kg) vs placebo (0.9% saline)

- Patients > 18 yrs with symptomatic infection who were receiving SOC (either metro/vanc)

- 30 sites in US and Canada

- **Primary outcome:** Recurrence of infection during 84d after administration of drug or placebo
Phase 2 trial evidence for toxin-directed HuMabs

Secondary end points:
• Number of days to resolution of initial episode
• Severity of initial episode
• Failure of antibiotic treatment
• Serum levels of antitoxin antibodies by ELISA
Efficacy

rCDI in 32/200 patients:
7% antibody group; 25% placebo group (95% CI, 7-29; P<0.001)

RR of rCDI significantly lower in antibody group, 0.23 (95% CI, 0.08 to 0.54; P<0.01)

Figure 1. Time to Recurrence of *Clostridium difficile* Infection (CDI).
The cumulative percentages of 32 patients with laboratory-documented recurrent CDI during the 84-day study period are shown for the two study groups: 7% in the antibody group and 25% in the placebo group. Five patients had a second episode of CDI recurrence: two in the antibody group and three in the placebo group. The P value was calculated by means of the log-rank test.
Subgroup analyses

CDA1-CDB1 treatment effective with:

- Metronidazole or Vancomycin
- Epidemic strain BI/NAP1/027 or non-epidemic strains
- Patients with 1st episode or those with multiple previous episodes

**Table 2. Recurrence of Clostridium difficile Infection (CDI), According to Subgroup.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monoclonal Antibody (N=101)</th>
<th>Placebo (N=99)</th>
<th>Difference in Rate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. with recurrence/total no. (%)</td>
<td>percentage points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization status at enrollment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>7/50 (14)</td>
<td>13/52 (25)</td>
<td>11 (-5 to 27)</td>
<td>0.21</td>
</tr>
<tr>
<td>Outpatient</td>
<td>0/51</td>
<td>12/47 (26)</td>
<td>26 (14 to 40)</td>
<td>&lt;0.001</td>
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<tr>
<td>Antibiotic treatment at enrollment</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>3/30 (10)</td>
<td>7/22 (32)</td>
<td>22 (-1 to 46)</td>
<td>0.08</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>4/71 (6)</td>
<td>18/77 (23)</td>
<td>17 (6 to 29)</td>
<td>0.003</td>
</tr>
<tr>
<td>Presence of BI/NAP1/027 strain at enrollment*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2/25 (8)</td>
<td>6/19 (32)</td>
<td>24 (1 to 50)</td>
<td>0.06</td>
</tr>
<tr>
<td>No†</td>
<td>4/52 (8)</td>
<td>11/55 (20)</td>
<td>12 (-1 to 26)</td>
<td>0.09</td>
</tr>
<tr>
<td>No. of previous CDI episodes‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>2/29 (7)</td>
<td>12/32 (38)</td>
<td>31 (10 to 50)</td>
<td>0.006</td>
</tr>
<tr>
<td>Single</td>
<td>5/72 (7)</td>
<td>12/66 (18)</td>
<td>11 (0 to 23)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Serum antibodies against toxins A and B

‘x’ = antitoxin ab levels at time of CDI recurrence for each of 32 patients (7 in ab group and 25 in placebo group)

NB: high levels of neutralising anti-toxin antibodies in 7 patients with recurrence in antibody group

? Impaired local or other systemic host immune mechanisms

? Inadequate levels in intestinal mucosa
Other endpoints

- No significant differences between antibody group and placebo group in:
  - Severity of diarrhoea during initial episode of CDI
  - Median or mean number of days to resolution of initial episode
  - Proportion of patients in whom treatment failed

- Post-hoc analyses
  - Proportion of patients admitted to hospital after study infusion: 9% antibody group; 20% placebo group (P = 0.03)
Adverse events

- No significant differences between groups except fewer reports of hypotension in antibody group

Deaths during study period:
- No deaths attributable to study drug
  - 7 in antibody group
  - 8 in placebo group

### Table 3. Most Common Grade 3 or 4 Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Monoclonal Antibody (N = 101)</th>
<th>Placebo (N = 99)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>3 (3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiorespiratory arrest</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0.62</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>4 (4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>3 (3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>6 (6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Leukocytosis‡</td>
<td>0</td>
<td>4 (4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>4 (4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sepsis or septic shock</td>
<td>1 (1)</td>
<td>5 (5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>3 (3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Not serious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (3)</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (5)</td>
<td>12 (12)</td>
<td>0.08</td>
</tr>
<tr>
<td>Leukocytosis‡</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (3)</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>3 (3)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Antibodies to Toxin B Are Protective Against *Clostridium difficile* Infection Recurrence

Swati B. Gupta,1 Vinay Mehta,2 Erik R. Dubberke,3 Xuemei Zhao,4 Mary Beth Dorr,5 Danya Guris,5 Deborah Molrine,6,7 Mark Leney,2,8 Mark Miller,9 Marilyne Dupin,10 and T. Christopher Mast2

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Odds Ratio</th>
<th>Univariate P Value</th>
<th>Odds Ratio</th>
<th>Multivariable P Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>.038</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&lt;65 y/≥65 y)</td>
<td>3.93</td>
<td>.009</td>
<td>3.76</td>
<td>.024</td>
</tr>
<tr>
<td>Female vs male sex</td>
<td>1.02</td>
<td>.971</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Other” race vs white race</td>
<td>0.70</td>
<td>.613</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horn index 3 vs Horn index 1</td>
<td>3.12</td>
<td>.176</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horn index 2 vs Horn index 1</td>
<td>4.20</td>
<td>.077</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole vs vancomycin</td>
<td>0.65</td>
<td>.424</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional antibiotic use</td>
<td>2.20</td>
<td>.095</td>
<td>2.06</td>
<td>.19</td>
</tr>
<tr>
<td>Antacids/antulcer use</td>
<td>0.92</td>
<td>.870</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior episodes of CDI (yes/no)</td>
<td>2.7</td>
<td>.041</td>
<td>2.58</td>
<td>.09</td>
</tr>
<tr>
<td>Inpatient vs outpatient</td>
<td>0.97</td>
<td>.952</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MassBiologics assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of toxin A antibodies (yes/no)</td>
<td>0.46</td>
<td>.461</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of toxin B antibodies (yes/no)</td>
<td>0.12</td>
<td>.045</td>
<td>0.11</td>
<td>.05</td>
</tr>
<tr>
<td>Presence of toxin A and toxin B</td>
<td></td>
<td></td>
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<td></td>
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</table>
Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection

<table>
<thead>
<tr>
<th>Trial</th>
<th>MODIFY 1 (NCT01241552)</th>
<th>MODIFY II (NCT01513239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Merck Sharpe and Dohme</td>
<td>Merck Sharp and Dohme</td>
</tr>
<tr>
<td>Location</td>
<td>322 sites in 30 countries</td>
<td>322 sites in 30 countries</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Randomised, double-blind, placebo-controlled</td>
</tr>
<tr>
<td>Participants</td>
<td>N= 1,452; aged ≥ 18 yrs, CDI receiving SOC</td>
<td>N= 1,203; aged ≥ 18 yrs, CDI receiving SOC</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to: actoxumab 10mg/kg; bezlotoxumab 10mg/kg; actoxumab 10mg/kg + bezlotoxumab 10mg/kg; or placebo: all as single IV infusion with SOC</td>
<td>Randomised to bezlotoxumab 10mg/kg; actoxumab 10mg/kg + bezlotoxumab 10mg/kg; or placebo: all as single IV infusion with SOC</td>
</tr>
<tr>
<td>Follow up</td>
<td>Single treatment; 12 weeks</td>
<td>Single treatment; 12 weeks 12 mths in subset</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>No. of patients with rCDI</td>
<td>No. of patients with rCDI</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Sustained clinical cure</td>
<td>Sustained clinical cure</td>
</tr>
</tbody>
</table>
Key Results

Figure 1. Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.
The results shown are for the modified intention-to-treat population, which included all randomly assigned participants who received the study infusion, had a baseline stool test that was positive for toxigenic *C. difficile*, and started receiving standard-of-care therapy before or within 1 day after receiving the monoclonal antibodies. *P* values were calculated by the Miettinen and Nurminen method, with stratification according to trial, standard-of-care therapy, and hospitalization status.
### Efficacy endpoints

Table 1: Efficacy of a single intravenous infusion of bezlotoxumab 10 mg/kg in preventing recurrence of *C. difficile* infection in adults receiving standard-of-care antibacterial therapy in phase 3 trials and their pooled analysis [17]

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MODIFY 1</th>
<th>MODIFY 2</th>
<th>Pooled</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>BEZ (n = 386)</td>
<td>PL (n = 395)</td>
<td>BEZ (n = 395)</td>
</tr>
<tr>
<td>CDI recurrence (% of mITT pts)</td>
<td>17**</td>
<td>28</td>
<td>16**</td>
</tr>
<tr>
<td>CDI recurrence in mITT pts with initial clinical cure (% pts)</td>
<td>22*</td>
<td>33</td>
<td>19***</td>
</tr>
<tr>
<td>Initial clinical cure (% of mITT pts)</td>
<td>77</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Sustained clinical cure (% of mITT pts)</td>
<td>60</td>
<td>55</td>
<td>67***</td>
</tr>
</tbody>
</table>

Deek ED et al 2017 *Drugs*; 77: 1657-1663
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Bezlotoxumab (n)</th>
<th>Placebo (n)</th>
<th>Rate Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>129/781 (16.5%)</td>
<td>206/773 (26.6%)</td>
<td>-10.0 (-37.5%)</td>
</tr>
<tr>
<td>Risk factors for recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 yr of age</td>
<td>60/390 (15.4%)</td>
<td>127/405 (31.4%)</td>
<td>-16.0 (-50.9%)</td>
</tr>
<tr>
<td>No CDI in past 6 mo</td>
<td>75/556 (13.5%)</td>
<td>114/545 (20.9%)</td>
<td>-7.4 (-35.5%)</td>
</tr>
<tr>
<td>≥1 CDI episodes in past 6 mo</td>
<td>54/216 (25.0%)</td>
<td>90/219 (41.1%)</td>
<td>-16.1 (-39.2%)</td>
</tr>
<tr>
<td>≥2 previous CDI episodes ever</td>
<td>29/100 (29.0%)</td>
<td>53/126 (42.1%)</td>
<td>-13.1 (-31.1%)</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>26/178 (14.6%)</td>
<td>42/153 (27.5%)</td>
<td>-12.8 (-46.8%)</td>
</tr>
<tr>
<td>Severe CDI: Zar score ≥2</td>
<td>13/122 (10.7%)</td>
<td>28/125 (22.4%)</td>
<td>-11.7 (-52.4%)</td>
</tr>
<tr>
<td>027, 078, or 244 strain</td>
<td>22/102 (21.6%)</td>
<td>37/115 (32.2%)</td>
<td>-10.6 (-33.0%)</td>
</tr>
<tr>
<td>027 strain</td>
<td>21/89 (23.6%)</td>
<td>34/100 (34.0%)</td>
<td>-10.4 (-30.6%)</td>
</tr>
<tr>
<td>Stratification variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>73/530 (13.8%)</td>
<td>120/520 (23.1%)</td>
<td>-9.3 (-40.3%)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>56/251 (22.3%)</td>
<td>86/253 (34.0%)</td>
<td>-11.7 (-34.4%)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>56/379 (14.8%)</td>
<td>85/374 (22.7%)</td>
<td>-8.0 (-35.0%)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>67/372 (18.0%)</td>
<td>114/373 (30.6%)</td>
<td>-12.6 (-41.1%)</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>6/30 (20.0%)</td>
<td>7/26 (26.9%)</td>
<td>-6.9 (-25.7%)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>69/354 (19.5%)</td>
<td>106/366 (29.0%)</td>
<td>-9.5 (-32.7%)</td>
</tr>
<tr>
<td>Europe</td>
<td>47/313 (15.0%)</td>
<td>71/293 (24.2%)</td>
<td>-9.2 (-38.0%)</td>
</tr>
<tr>
<td>Asia–Pacific</td>
<td>11/79 (13.9%)</td>
<td>21/77 (27.3%)</td>
<td>-13.3 (-48.9%)</td>
</tr>
<tr>
<td>Latin America</td>
<td>2/30 (6.7%)</td>
<td>8/35 (22.9%)</td>
<td>-16.2 (-70.8%)</td>
</tr>
</tbody>
</table>
Adverse events

• Comparable across bezlotoxumab and placebo arms
• Adverse events, serious adverse events, and deaths higher in actoxumab group
• Safety signal: heart failure
  • Among patients with congestive heart failure, SAE was recorded in 12.7% of bezlotoxumab recipients (15/118) c/w 4.8% (5/104) of placebo group
  • 19.5% (23/118) and 12.5% (13/104) of this subgroup died, with varied cause of death
  • Use bezlotoxomab with CHF only when benefit outweighs risk
Post-hoc analyses:
high risk populations

1 Risk factor:
AR – 16%
RR – 43%

≥3 Risk factors:
AR – 24.8%
RR – 54%
<table>
<thead>
<tr>
<th>CDI Hx and severe CDI</th>
<th>Bezlotoxumab % (n/N)</th>
<th>Placebo % (n/N)</th>
<th>Difference (%)</th>
<th>Absolute Difference % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14.3 (2/14)</td>
<td>50.0 (10/20)</td>
<td>-35.7</td>
<td>-71.4</td>
</tr>
</tbody>
</table>

CDI Hx=history of CDI within the previous 6 months.
## Other outcomes

### Table 2. Other Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bezlotoxumab</th>
<th>Placebo</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Risk Factors</td>
<td>≥1 Risk Factor</td>
<td>No Risk Factors</td>
<td>≥1 Risk Factor</td>
</tr>
<tr>
<td><strong>FMT during follow-up</strong></td>
<td>n = 189</td>
<td>n = 592</td>
<td>n = 190</td>
<td>n = 583</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
<td>7 (1.2)</td>
<td>5 (2.6)</td>
<td>18 (3.1)</td>
</tr>
<tr>
<td><strong>30-day readmissions</strong></td>
<td>n = 99</td>
<td>n = 433</td>
<td>n = 98</td>
<td>n = 422</td>
</tr>
<tr>
<td></td>
<td>20 (21.1)</td>
<td>102 (22.7)</td>
<td>30 (20.4)</td>
<td>132 (20.4)</td>
</tr>
<tr>
<td><strong>All-cause</strong></td>
<td>n = 99</td>
<td>n = 433</td>
<td>n = 98</td>
<td>n = 422</td>
</tr>
<tr>
<td></td>
<td>2 (2.1)</td>
<td>25 (5.7)</td>
<td>4 (4.1)</td>
<td>54 (12.8)</td>
</tr>
<tr>
<td><strong>CDI-associated</strong></td>
<td>n = 189</td>
<td>n = 597</td>
<td>n = 192</td>
<td>n = 569</td>
</tr>
<tr>
<td></td>
<td>2 (1.1)</td>
<td>25 (4.2)</td>
<td>3 (1.6)</td>
<td>24 (4.1)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>n = 189</td>
<td>n = 597</td>
<td>n = 192</td>
<td>n = 569</td>
</tr>
<tr>
<td></td>
<td>6 (3.2)</td>
<td>48 (8.0)</td>
<td>6 (3.1)</td>
<td>53 (9.0)</td>
</tr>
</tbody>
</table>
Number needed to treat

- NNTs for preventing 1 episode of rCDI and sustained clinical cure at 12 weeks (10 and 11 respectively)

- NNTs for prevention of recurrence were lower in:
  - >65 yrs - NNTs 7
  - Previous CDI in preceding 6/12 - NNTS 7
  - Immunocompromised – NNTs 8
  - Severe CDI – NNTs 9

BUT actual NNT may differ in clinical practice
NNT to prevent recurrence likely will be higher than that seen in clinical trials for populations in which PCR is the primary diagnostic test
Cost effectiveness analysis

Bezlotoxumab
• 1 vial 1,000 mg in person <100kg = £2,470 (MSD, 2017)
• Does not include VAT, local procurement discounts or administrative costs incurred

Competitors
• Fidaxomicin: 200mg bd x 10 day course £1,350
• Vancomycin: 125 mg qds x 10-14 day course £126-280
Cost-effectiveness of Bezlotoxumab Compared With Placebo for the Prevention of Recurrent Clostridium difficile Infection

Vimalanand S. Prabhu,1 Erik R. Dubberke,2 Mary Beth Dorr,1 Elamin Elbasha,1 Nicole Cossrow,1 Yiling Jiang,3 and Stephen Marcella1

†Merck & Co. Inc., Kenilworth, New Jersey; ‡Washington University, St. Louis, Missouri; and §Merck Sharp & Dohme Ltd., Hoddesdon, Hertfordshire, United Kingdom

Markov health transition model
Bezlotoxumab is cost-effective in prevention or rCDI c/w placebo, among patients receiving SOC antibiotics

NB: No head-to-head cost-effective analyses conducted for fidaxomicin or FMT
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Incremental Total Recurrence (Bezlotoxumab – Placebo)</th>
<th>NNT to Prevent a Recurrence</th>
<th>Incremental Mortality (Bezlotoxumab – Placebo)</th>
<th>Incremental Costs, $ (Bezlotoxumab – Placebo)</th>
<th>Incremental QALYs (Bezlotoxumab – Placebo)</th>
<th>ICER, $/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients aged ≥65 y</td>
<td>-26.4%</td>
<td>3.8</td>
<td>-1.7%</td>
<td>1662</td>
<td>0.11</td>
<td>15298</td>
</tr>
<tr>
<td>Patients who are immunocompromised</td>
<td>-21.2%</td>
<td>4.7</td>
<td>-1.4%</td>
<td>2081</td>
<td>0.17</td>
<td>12597</td>
</tr>
<tr>
<td>Patients with severe CDI on presentation</td>
<td>-19.5%</td>
<td>5.1</td>
<td>-1.2%</td>
<td>2228</td>
<td>0.10</td>
<td>21430</td>
</tr>
<tr>
<td>Patients aged ≥65 y and ≥1 previous episode in prior 6 mo</td>
<td>-39.7%</td>
<td>2.5</td>
<td>-2.6%</td>
<td>587</td>
<td>0.16</td>
<td>3591</td>
</tr>
<tr>
<td>Patients who are immunocompromised and ≥1 previous episode in prior 6 mo</td>
<td>-33.0%</td>
<td>3.0</td>
<td>-2.1%</td>
<td>1127</td>
<td>0.23</td>
<td>4979</td>
</tr>
<tr>
<td>Patients with severe CDI on presentation and ≥1 previous episode in prior 6 mo</td>
<td>-40.2%</td>
<td>2.5</td>
<td>-2.5%</td>
<td>555</td>
<td>0.19</td>
<td>2938</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, *Clostridium difficile* infection; ICER, incremental cost-effectiveness ratio; NNT, number needed to treat; QALY, quality-adjusted life-year.
Suggested target population

- Older adults (≥65 yrs)
- Patients with previous CDI episode(s)
- Immunosuppressed hosts
- Hypervirulent strains
- Patients with severe CDI
- Patients who frequently receive antibiotics for chronic conditions or those scheduled for surgery
- Long term care residents
- Patients admitted to hospital during a CDI outbreak
Unanswered questions

• What is the specific time-interval for infusion in correlation to SOC CDI therapy?
• What serum target levels required to achieve effective intestinal luminal concentration against toxin B?
• How will mAbs fare against fidaxomicin and FMT?
• Which other at-risk populations are likely to benefit for be:
New trials

• NCT03182907 - MODIFY III
  • *Bezlotoxumab vs placebo in children (aged 1-18 yrs) with CDI*

• NCT03756454
  • *Comparing effectiveness of bezlotoxumab vs placebo in decreasing morbidity and mortality in patients with fulminant CDI requiring surgery*

• NCT03880539
  • *Bezlotoxumab in addition to SOC vancomycin for treatment of multi-recurrent CDI*

• NCT03829475
  • *ICON-2: FMT and bezlotoxumab compared to FMT and placebo for patients with IBD and CDI*
Future considerations

• Next generation antibody therapeutics
  • Smaller antibody formats
    • Single domain antibodies
    • Bispecific or multispecific recombinant antibodies against the toxins
  • Engineered lactobacilli to produce variable domains of heavy chain only antibodies against CD toxins

• Improved delivery systems
  • Oral antibodies
Thank you