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Effect of endogenous Clostridium difficile toxin antibodies on recurrence of C. difficile infection

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Key points (40/40 words):

- High titers of endogenous antibodies to Clostridium difficile toxin B, but not toxin A, were associated with reduced recurrence of C. difficile infection.
- These findings are consistent with efficacy data from the Phase 3 MODIFY trials of bezlotoxumab and actoxumab.

Abstract (248/250 words)

Background: Endogenous antibodies (eAb) against Clostridioides (Clostridium) difficile toxins may protect against recurrence of C. difficile infection (rCDI). This hypothesis was tested using placebo group data from MODIFY (MOnoclonal antibodies for C. DIFficile therapY) I (NCT01241552) and MODIFY II (NCT01513239), global, randomized Phase 3 trials that assessed the efficacy and safety of the anti-toxin monoclonal antibodies bezlotoxumab and actoxumab in participants receiving antibiotic therapy for CDI.

Methods: A placebo infusion (normal saline) was administered on study Day 1. Serum samples were collected on Day 1, Week 4, and Week 12, and eAb-A and eAb-B titers measured by two validated electrochemiluminescence immunoassays. Rates of initial clinical cure and rCDI were summarized by eAb titer category (low, medium, high) at each time point.

Results: Serum eAb titers were available from a total of 773 participants. The proportion of participants with high eAb-A and eAb-B titers increased over time. Rates of initial clinical cure were similar across eAb titer categories. There was no correlation between eAb-A titers and rCDI rate at any time point. However, there was a negative correlation between rCDI and eAb-B titer on Day 1 and Week 4. rCDI occurred in 22% of participants with high eAb-B titers at baseline compared with 35% with low or medium titers ($p = 0.015$).

Conclusion: Higher eAb titers against toxin B, but not toxin A, were associated with protection against rCDI. These data are consistent with the observed efficacy of bezlotoxumab, and lack of efficacy of actoxumab, in the MODIFY trials.

Introduction

Clostridioides (Clostridium) difficile infection (CDI) is a major cause of gastrointestinal morbidity [1, 2]. Most cases of CDI resolve following antibacterial treatment with oral vancomycin, fidaxomicin, or metronidazole [3, 4]; however, CDI recurrence (rCDI) following initial therapy occurs in up to 25% of cases [5, 6].

The fully human monoclonal antibody (mAb) bezlotoxumab binds to and neutralizes C. difficile toxin B [7, 8]. It is approved in the United States and Europe for the prevention of rCDI in adults receiving antibacterial drug treatment for CDI who are at high risk for recurrence [9, 10]. The global Phase 3 trials MODIFY (MOnoclonal antibodies for C. DIFficile therapY) I and MODIFY II demonstrated the efficacy of bezlotoxumab vs placebo in reducing rates of rCDI in participants receiving antibacterial drug treatment for CDI [11]. In the MODIFY trials, administration of the C. difficile-toxin-A–neutralizing mAb, actoxumab, was not efficacious alone and did not improve efficacy when given with bezlotoxumab [11].

Consistent with the observed efficacy of bezlotoxumab, prior studies have indicated that low serum anti-toxin antibody levels may be associated with an increased risk of rCDI [12-16]. However, the number of participants in previous investigations was modest, typically <60 per study.

The aim of this pre-specified exploratory analysis was to determine the relationship between levels of endogenous anti-toxin A (eAb-A) and anti-toxin B (eAb-B) antibodies and the risk of rCDI using pooled data from the placebo groups of the MODIFY I/II trials. This CDI case cohort is the largest single dataset examined in the field. It was hypothesized that participants with low baseline levels of eAb-A or eAb-B may be at greater risk of rCDI than participants with moderate or high eAb levels at baseline.

Methods

Study design

MODIFY I (NCT01241552) and MODIFY II (NCT01513239) were randomized, double-blind, placebo-controlled, Phase 3 trials that were conducted from November 1, 2011 through May 22, 2015 at 322 sites in 30 countries [11]. Both trials were conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. Institutional review board or independent ethics committee approval of protocols and amendments was obtained at each study site, and all participants provided written informed consent before the trials began.

All participants (≥18 years of age) were treated with antibacterial drug treatment for primary or recurrent CDI with an intended duration of 10 to 14 days, during which time they received a single infusion of 10 mg/kg bezlotoxumab alone, 10 mg/kg actoxumab alone (MODIFY I only), bezlotoxumab + actoxumab (both 10 mg/kg), or placebo (normal saline). CDI was defined as diarrhea (≥3 unformed bowel movements [Types 5 to 7 on the Bristol stool scale] in 24 hours), associated with a stool test result positive for toxigenic C. difficile. Participants recorded the number of unformed bowel movements daily over the 12-week study period. Serum samples were collected pre-dose (Day 1), and at Weeks 4 and 12 post-dose for measurement of eAb-A and eAb-B.

Assessments

Efficacy assessments were performed on the modified intent-to-treat population, which included all randomized participants who received the study infusion, had a positive baseline stool test for toxigenic C. difficile, and began receiving antibacterial drug treatment for CDI before or within one day after randomization. CDI recurrence was defined as a new episode of diarrhea associated with a positive stool test for toxigenic C. difficile in participants who achieved initial clinical cure of the baseline CDI episode (clinical cure population). Initial clinical cure was defined as no diarrhea during the 2 consecutive days following completion of antibacterial drug treatment for CDI (administered for ≤16 days).

Endpoints

The primary efficacy endpoint of MODIFY I and MODIFY II was the proportion of participants who experienced rCDI within 12 weeks of antibody or placebo infusion.

Endogenous antibody analysis

In this analysis, only participants randomized to the placebo groups of MODIFY I or MODIFY II with available serum eAb titer results were included. Antibody titers for eAb-A and eAb-B were measured using two validated electrochemiluminescence immunoassays with full-length C. difficile toxin A or B, respectively, as the capture reagent, as previously described [17]. Results were reported as <1:1000, 1:1000, 1:5000, 1:25,000, and ≥1:125,000. As there is no clearly defined immunological surrogate of efficacy for rCDI tied to a specific eAb-A or eAb-B level, eAb levels were arbitrarily categorized as low (≤1:1000), medium (1:5000), or high (≥1:25,000).

Statistical analysis

The proportion of participants who experienced rCDI was summarized by eAb category at Day 1 and at Week 4. A two-sided Cochran-Armitage trend test was performed to evaluate correlations between eAb-A / eAb-B titer category and rCDI. Additionally, to evaluate potential correlations between demographic and clinical characteristics and Day 1 eAb-B titer category, a two-sided or one-sided Cochran-Armitage trend test was performed. No adjustments for multiplicity were made and p-values of <0.05 were considered statistically significant due to the exploratory nature of this analysis. Differences in the proportion of participants with rCDI in low versus medium plus high levels of eAb-A or eAb-B titers were evaluated using a two-sided Fisher's exact test.

Results

Study participants

Of the 773 participants in MODIFY I and MODIFY II who were randomized to placebo treatment, almost all had serum titer results for both antibodies on Day 1; 755 (97.7%) and 751 (97.2%) had

measurements of eAb-A and eAb-B titers, respectively. At Week 4, 656 (84.9%) and 654 (84.6%) had measurements of eAb-A and eAb-B titers, respectively. At the end of the 12-week study period, 595 (77.0%) and 592 (76.6%) participants had results for eAb-A and eAb-B titer analysis, respectively.

Changes in eAb profile over time

On Day 1, 37.5% of participants had low antibody titers of eAb-A (**Figure 1A**), 38.3% had low antibody titers of eAb-B (**Figure 1B**), and 21.3% had low antibody titers of both antibodies (not shown). The proportion of participants with low eAb-A and eAb-B titers decreased by Week 12 (**Figure 1A, 1B**). Conversely, the proportion of participants with high titers of eAb-A and eAb-B titers increased with time (two-sided Cochran-Armitage test $p = 0.0014$ and $p = 6.12 \times 10^{-13}$, respectively) (**Figure 1A, 1B**).

Effect of eAb titer on initial clinical cure and CDI recurrence

Initial clinical cure rates were similar across participants with low, medium, and high baseline titers of eAb-A and eAb-B (**Figure 2)**. Results of a two-sided Cochran-Armitage trend test showed there was no statistically significant correlation between the proportion of participants experiencing rCDI and eAb-A titer category at Day 1 ($p = 0.382$) or Week 4 ($p = 0.178$) (**Figure 3**). However, there was a negative correlation between the rate of rCDI and eAb-B titer category at Day 1 (two-sided Cochran-Armitage trend test [$p = 0.003$]) and Week 4 (two-sided Cochran-Armitage trend test [$p = 0.064$] and one-sided "increasing" Cochran-Armitage trend test [$p = 0.032$]) (**Figure 3**). Among participants with high eAb-B titer at Day 1, 23/104 (22.1%) experienced rCDI, while for those with low or medium eAb-B titer at Day 1, rCDI occurred in 177/500 (35.4%) of participants (two-sided Fisher's exact test $p = 0.015$).

Influence of demographic factors on eAb profile

The demographics and baseline disease characteristics of the participants, stratified by Day 1 antibody titer of eAb-B, are shown in **Table 1**. Low Day 1 eAb-B levels were found in a greater proportion of immunocompromised participants compared with non-immunocompromised participants (49.6% vs

35.7%, two-sided Fisher's exact test p = 0.0028). Participants with no previous CDI episode ever or no episode within the previous 6 months were more likely to have low Day 1 eAb-B levels compared with those who had at least 1 previous CDI episode ever or within 6 months (42.6% and 41.0% vs 29.9% and 30.5%; two-sided Fisher's exact test p = 0.00078 and 0.0076, respectively). Demographics and baseline disease characteristics of participants stratified by Day 1 eAb-A titer are not shown as there was no correlation between rCDI and Day 1 eAb-A titer category.

Other variables associated with low Day 1 eAb-B titer were severe CDI vs not severe CDI (48.4% vs 36.3%; two-sided Fisher's exact test p = 0.015), and inpatient vs outpatient at time of randomization (41.9% vs 31.2%; two-sided Fisher's exact test p = 0.0051).

There was a trend for advanced age, a known risk factor for recurrent CDI, to be a predictor of low eAb-B titers, as the proportion of participants under 50 years of age with low eAb-B titers was 33.8%, whereas a higher proportion of participants aged over 50 years had low eAb-B titers: 50-64 years (40.5%), 65-80 years (39.7%), and ≥80 years (37.8%) although these differences were not statistically significant (two-sided Fisher's exact test p = 0.22).

Discussion

Correlation of anti-toxin–mediated protection from CDI infection and/or recurrence has previously been shown in clinical trials for serum antibodies against C. difficile toxin A [13, 15] and toxin B [14, 16]. In this analysis, titers of eAb-A and eAb-B increased over time following CDI, consistent with a convalescent humoral immune response to toxins A and B. Furthermore, high titers of eAb-B, but not eAb-A, were associated with reduced risk of rCDI, consistent with the efficacy of bezlotoxumab and lack of efficacy of actoxumab observed in the MODIFY trials [11], and supporting the proposed mechanism of action of bezlotoxumab, which neutralizes C. difficile toxin B in vitro [18].

Similar results linking eAb-B, but not eAb-A, to rCDI protection were reported in an analysis of the placebo group from the proof-of-concept Phase 2 trial for the development of actoxumab and bezlotoxumab [14], although other studies have suggested that eAb-A serum response does mediate

protective effects on CDI recurrence [12, 15]. It is possible that differences in assay selectivity or sensitivity could have contributed to some of these discrepancies. In this analysis, full-length toxin A and toxin B proteins were used as capture reagents, facilitating the capture of all polyclonal antibody species [17]. It is also possible that the presence of neutralizing antibodies will provide a better correlation with successful prevention of recurrent CDI.

Although there was an inverse correlation between eAb-B titers and rCDI rate, a fairly high proportion (22.1%) of participants with high eAb-B titers on Day 1 experienced rCDI. These findings highlight the importance of considering demographic and clinical risk factors, in addition to biomarkers, in the development of predictive models for rCDI. In this analysis, advanced age, a known risk factor for recurrent CDI, was found to be associated with low eAb-B titers. Other known risk factors for recurrent CDI include compromised immunity, history of CDI in the previous 6 months, severe CDI (Zar score ≥2) at time of randomization, and isolation of a strain associated with poor outcomes (ribotypes 027, 078, or 244) [19]. In a study by Gerding and colleagues, in the placebo group, recurrent CDI occurred in 20.9% of participants without a risk factor compared with 37.2% in participants with ≥ 1 risk factor. In addition, rCDI increased with number of risk factors; rCDI was 31.3% in participants with 1 risk factor compared with 46.1% in participants with ≥ 3 risk factors [19].

An advantage of toxin neutralization over antibiotics currently used for rCDI is that the normal microbiota are not disrupted, allowing the body's natural defense against C. difficile the opportunity to re-establish itself following a course of effective antibiotic treatment for the initial episode of CDI. Furthermore, an approach that focuses on toxin neutralization is technically not subject to the emergence of resistance, and anti-toxin antibodies can be administered to patients who are immunocompromised or who require continued systemic antibiotics for other infections.

The limitations of this pre-specified exploratory analysis must be considered when interpreting these data. The assays employed in this analysis measured polyclonal antibodies to C. difficile toxins A and B, and did not discriminate between neutralizing antibodies and non-functional antibodies. Therefore,

some participants categorized in the medium- or high-titer categories may have had a low proportion of neutralizing antibodies; conversely those classified as low-titer may have substantial toxin neutralizing activity. It is also possible that because the low, medium, and high tiers of antibody titers used in these analyses were defined arbitrarily, they may be of limited physiological relevance. An assay designed to measure neutralizing antibodies may provide better predictive value than the assays used in this analysis.

In conclusion, the results of this exploratory analysis and the MODIFY trials suggest that antibodies to toxin B may play a more important role than antibodies to toxin A in protection against rCDI in humans. Although low eAb-B titers are correlated with risk for rCDI, our analysis suggests that eAb-B titers measured by this electrochemiluminescence immunoassay are of marginal utility as a biomarker for risk of CDI recurrence and are unlikely to improve predictive value over readily available clinical and demographic characteristics such as advanced age, compromised immunity, and CDI history [20-22].

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Conflict of Interests

JS, XZ, OFL, RR, DG, and MBD are employees of Merck Sharp & Dohme Corp. (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options in the company.

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DNG holds patents for the treatment and prevention of CDI; is an advisory board member for MSD, Actelion, Rebiotix, and Summit; and is a consultant for Da Volterra, Pfizer, and Sanofi Pasteur. He holds research grants from Seres Therapeutics, CDC, and the Department of Veterans Affairs Research Service.

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Table 1. Participant demographics and characteristics by Day 1 eAb-B titer category (mITT population)

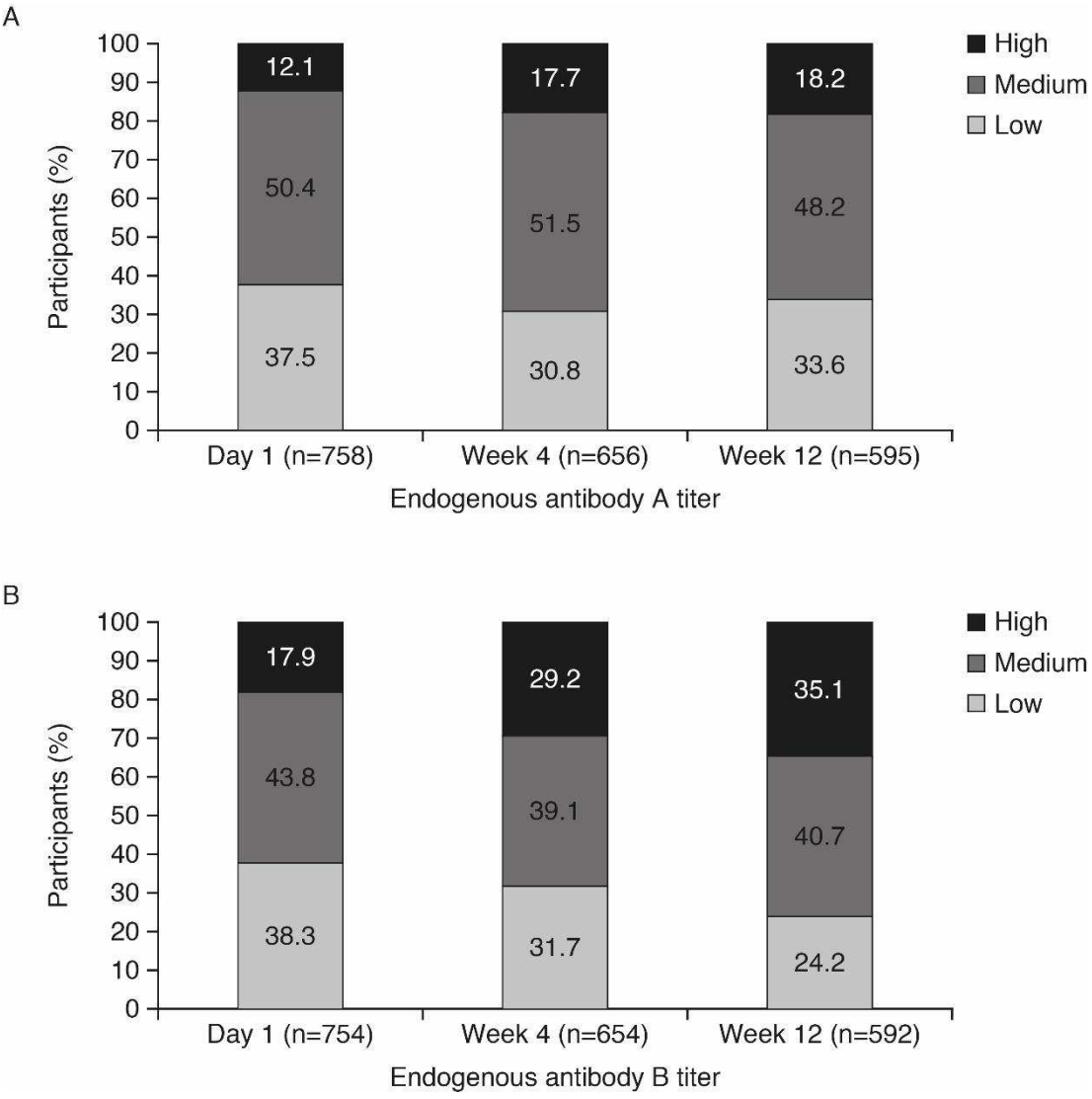
	eAb-B titer category			
	Low	**Medium**	**High**	**p-value[a]**
N (%)	288 (38.3)	328 (43.7)	135 (18.0)	
Female	174 (39.7)	181 (41.3)	83 (18.9)	0.856
Male	114 (36.4)	147 (47.0)	52 (16.6)	
Median age (range), years	66 (19-98)	66 (19-96)	64 (18-96)	
<50 years of age	51 (33.8)	69 (45.7)	31 (20.5)	0.175
50-64 years of age	83 (40.5)	83 (40.5)	39 (19.0)	0.800
65-80 years of age	98 (39.7)	114 (46.2)	35 (14.2)	0.173
≥80 years of age	56 (37.8)	62 (41.9)	30 (20.3)	0.598
≥1 CDI episodes in past 6 months	65 (30.5)	107 (50.2)	41 (19.2)	0.034[b]
No CDI episodes in past 6 months	217 (41.0)	220 (41.6)	92 (17.4)	
≥1 previous CDI episodes ever	75 (29.9)	122 (48.6)	54 (21.5)	0.001[b]
No previous CDI episodes ever	206 (42.6)	201 (41.5)	77 (15.9)	
Baseline episode severe (Zar score ≥2)	60 (48.4)	43 (34.7)	21 (16.9)	
Baseline episode not severe (Zar score <2)	216 (36.3)	272 (45.7)	107 (18.0)	0.065
Immunocompromised	70 (49.6)	47 (33.3)	24 (17.0)	0.025[b]
Not immunocompromised	218 (35.7)	281 (46.1)	111 (18.2)	
Inpatient	211 (41.9)	211 (41.9)	82 (16.3)	0.005[b]
Outpatient	77 (31.2)	117 (47.4)	53 (21.5)	
Charlson Comorbidity Index ≥3	108 (36.7)	129 (43.9)	57 (19.4)	0.357
Charlson Comorbidity Index <3	180 (39.4)	199 (43.5)	78 (17.1)	
Albumin ≤25 g/dL	52 (48.6)	38 (35.5)	17 (15.9)	0.064

Albumin >25 g/dL	232 (36.8)	284 (45.1)	114 (18.1)	
RT027	43 (43.9)	38 (38.8)	17 (17.3)	0.365
Other RTs	148 (39.9)	164 (44.2)	59 (15.9)	0.175
Unknown RTs	97 (34.4)	126 (44.7)	59 (20.9)	0.042

[a]2-sided Cochran-Armitage trend test significance level $p < 0.05$; [b]$p < 0.05$

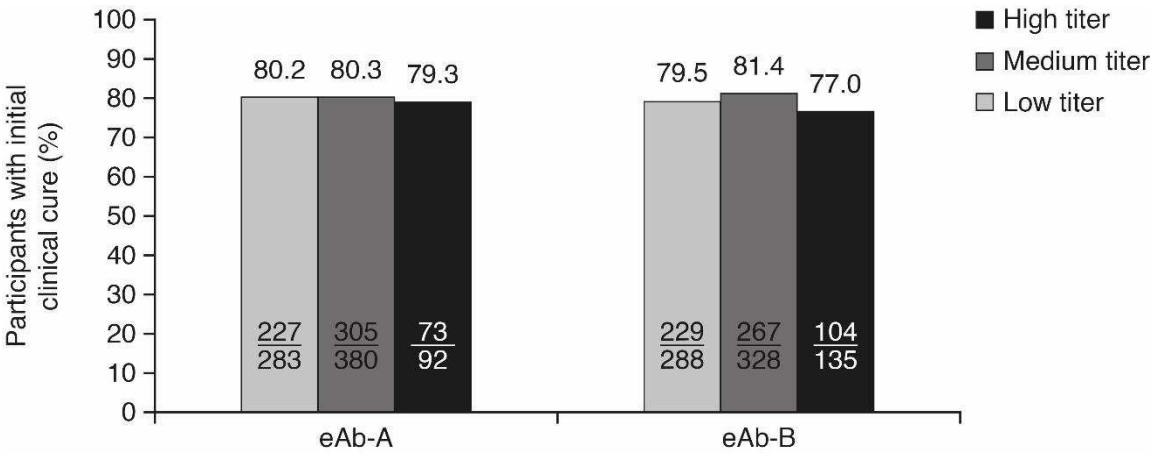
CDI, Clostridium difficile infection; eAb-B, endogenous anti-toxin B antibody; mITT, modified intent-to-treat; RT, ribotype

Figure 1. Distribution of participants by titer category at each measurement time point (A) by eAb-A titer and (B) by eAb-B titer (mITT population)



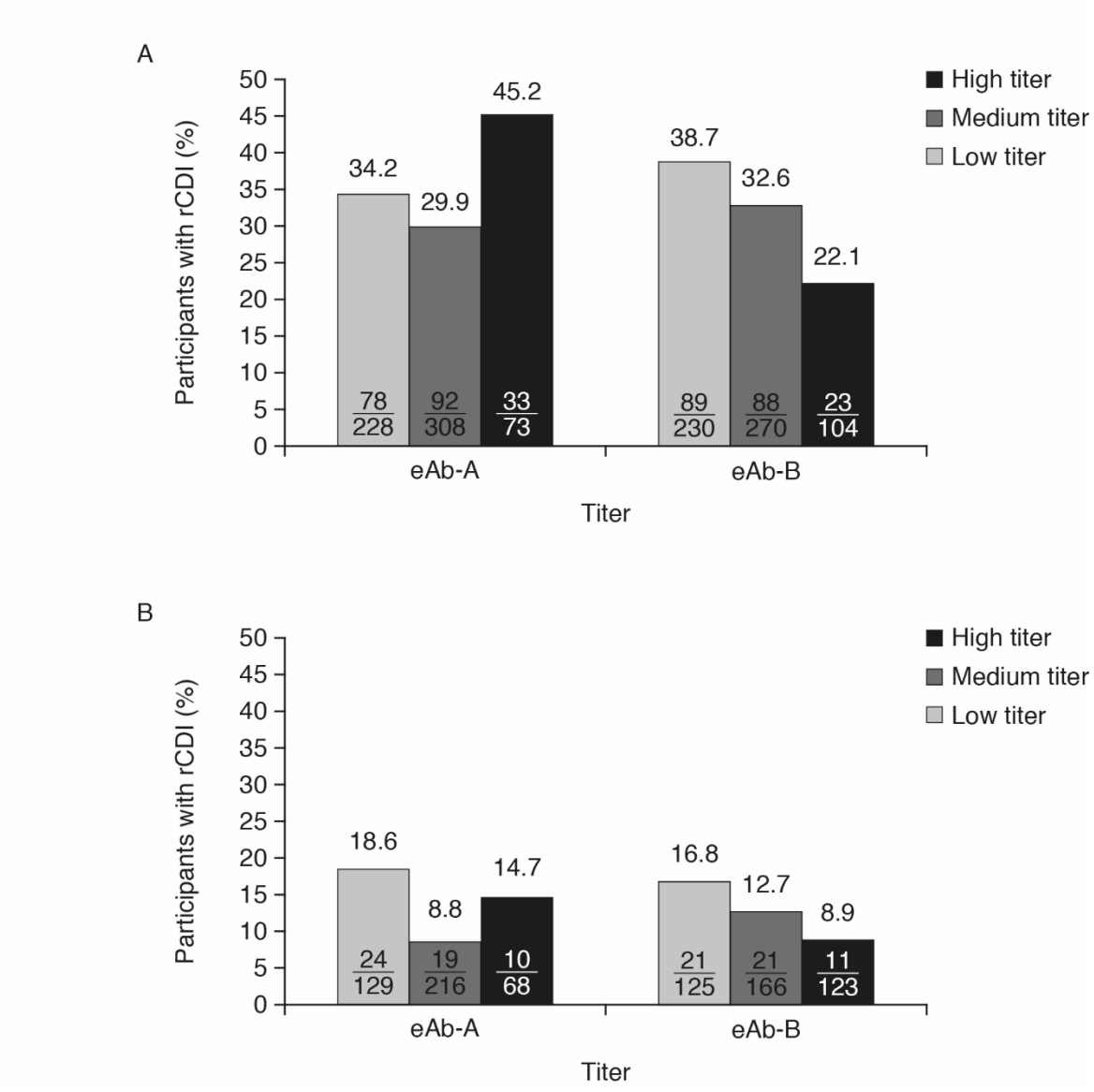
eAb-A, endogenous anti-toxin A antibody; eAb-B, endogenous anti-toxin B antibody; mITT, modified intent-to-treat

Figure 2. Proportion of participants with initial clinical cure by baseline eAb-A/eAb-B titer (mITT population)



eAb-A, endogenous anti-toxin A antibody; eAb-B, endogenous anti-toxin B antibody; mITT, modified intent-to-treat

Figure 3. Proportion of participants experiencing CDI recurrence through Week 12 (A) on Day 1 and (B) at Week 4 for eAb A and eAb B titers (clinical cure population)



CDI, Clostridium difficile infection; eAb-A, endogenous anti-toxin A antibody; eAb-B, endogenous anti-toxin B antibody; rCDI, Clostridium difficile infection recurrence