CRITICAL CARE

JOURNAL CLUB CRITIQUE

Clostridium difficile: moving beyond antimicrobial therapy

Amesh A Adalja[1,2] and John A Kellum*[1]

University of Pittsburgh Department of Critical Care Medicine: Evidence-Based Medicine Journal Club, edited by Sachin Yende

Expanded abstract

Citation

Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD, Jr., Leney M, Sloan S, Hay CA, Ambrosino DM: Treatment with monoclonal antibodies against Clostridium difficile toxins. *N Engl J Med* 2010, 362:197-205.

Background

New therapies are needed to manage the increasing incidence, severity, and high rate of recurrence of *Clostridium difficile* infection.

Methods

Objective: To assess the ability of monoclonal antibodies directed against two toxins of C.difficile to prevent recurrence of disease.

Design: Randomized, double-blind, placebo-controlled study

Setting: 30 medical centers in the United States and Canada

Subjects: 200 subjects with diarrhea and a positive stool toxin assay for *C.difficile* being treating with metronidazole or vancomycin

Intervention: Antibodies administered together as a single infusion, each at a dose of 10 mg per kilogram of body weight

Outcomes: The primary outcome was laboratory-documented recurrence of infection during the 84 days after the administration of monoclonal antibodies or placebo.

Results

Among the 200 patients who were enrolled (101 in the antibody group and 99 in the placebo group), the rate of recurrence of *C. difficile* infection was lower among patients treated with monoclonal antibodies (7% vs. 25%; 95% confidence interval, 7 to 29; P <0.001). The absolute risk reduction (ARR) was 16%, yielded a number needed to treat (NNT) of 5.5. The recurrence rates among patients with the epidemic BI/NAP1/027 strain were 8% for the antibody group and 32% for the placebo group (P = 0.06); among patients with more than one previous episode of *C. difficile* infection, recurrence rates were 7% and 38%, respectively (P = 0.006). The mean duration of the initial hospitalization for inpatients did not differ significantly between the antibody and placebo groups (9.5 and 9.4 days, respectively). At least one serious adverse event was reported by 18 patients in the antibody group and by 28 patients in the placebo group (P = 0.09).

Conclusions

The addition of monoclonal antibodies against *C. difficile* toxins to antibiotic agents significantly reduced the recurrence of *C. difficile* infection. (ClinicalTrials.gov number, NCT00350298 [ClinicalTrials.gov] .)

Commentary

Infection with *Clostridium difficile* places a significant burden on healthcare facilities. *C. difficile* has been shown to substantially increase hospital costs, hospital length of stay, and contribute to mortality [1,2]. One of the major factors hindering successful treatment of *C. difficile*-associated disease is the high rate of recurrence. Risk factors for recurrence include continued antibiotic use, antacid use, and older age [3]. Anecdotal evidence supports the use of several different modalities, such as tapering doses of vancomycin, rifaxamin, and fecal transplant. Yet, to date none of these therapies have been shown to be effective. Myriad risk factors for *C. difficile* infection coalesce in intensive care units, making it a highly relevant condition for intensivists.

The present study sought to evaluate the efficacy of an infusion of monoclonal antibodies directed towards the two principle toxins that emanate from *C. difficile* at preventing relapse of infection [4]. The study was a

*Correspondence: kellumja@upmc.edu
6th Floor Scaife Hall, 3550 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261, USA
Full list of author information is available at the end of the article

double blind, phase II, randomized, controlled trial at 30 medical centers in the US and Canada. This study enrolled 200 subjects between 2006 and 2008 with *C. difficile* infection in both inpatient and outpatient settings. All subjects were followed up for 84 days. Both study groups received antibiotic treatment with either metronidazole or vancomycin. The proportion of the hypervirulent BI/NAPI strain of *C. difficile* was similar in both the treatment and placebo arms. The study results revealed a significant decrease in the relapse rate of *C. difficile* in the treatment arm. The absolute risk reduction (ARR) was 18% and the number needed to treat (NNT) is 5.5. In those with more than one recurrence, the ARR of a recurrence was even greater (ARR = 31% and NNT = 3.2). There was no difference in the rates of serious adverse events between the placebo and treatment groups. However, the infusion failed to impact the severity of the initial episode of *C. difficile* infection or length of stay. All recurrences occurred in hospitalized subjects.

The study was well conducted and had few limitations. One limitation was that the study defined severity of *C. difficile* infection solely in terms of stool counts and may have unduly dismissed the benefit of the antibodies against the initial infection. Utilizing other parameters, such as quality of life and ability to tolerate meals, may have provided more information concerning the impact on the initial episode. Additionally, the exclusion of the sickest patients with *C. difficile* may have limited the generalizability of the study to acute care settings.

Recurrent *C. difficile*-associated disease is an important problem that not only affects the patient, but places others at risk from environmental contamination with the bacteria. The monoclonal antibodies studied in this paper provide hope that those plagued with recurrent infections can be treated effectively and safely. The utilization of monoclonal antibodies against infectious diseases is a crucial advance in developing specific therapies that are targeted at the organism of interest and not likely to inflict collateral damage to the patient's microbiome, an important point made in the editorial accompanying the study [5].

Recommendation

In conclusion, the addition of monoclonal antibodies did not alter the severity of *Clostridium difficile*-associated disease. However, monoclonal antibodies will reduce the recurrence of disease and should be routinely administered to those at highest risk for recurrence. Determining the cost-effectiveness of this approach remains to be seen.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA. [2]Center for Biosecurity of UPMC, Baltimore, MD.

Published: 16 September 2010

References

1. Dubberke ER, Butler AM, Reske KA, Agniel D, Olsen MA, D'Angelo G, McDonald LC, Fraser VJ: **Attributable outcomes of endemic Clostridium difficile-associated disease in nonsurgical patients.** *Emerg Infect Dis* 2008, **14:**1031-1038.
2. Dubberke ER, Reske KA, Olsen MA, McDonald LC, Fraser VJ: **Short- and long-term attributable costs of Clostridium difficile-associated disease in nonsurgical inpatients.** *Clin Infect Dis* 2008, **46:**497-504.
3. Garey KW, Sethi S, Yadav Y, DuPont HL: **Meta-analysis to assess risk factors for recurrent Clostridium difficile infection.** *J Hosp Infect* 2008, **70:**298-304.
4. Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD, Jr., Leney M, Sloan S, Hay CA, Ambrosino DM: **Treatment with monoclonal antibodies against Clostridium difficile toxins.** *N Engl J Med* 2010, **362:**197-205.
5. Kyne L: **Clostridium difficile--beyond antibiotics.** *N Engl J Med* 2010, **362:**264-265.

doi:10.1186/cc9249
Cite this article as: Adalja AA, Kellum JA: ***Clostridium difficile*: moving beyond antimicrobial therapy.** *Critical Care* 2010, **14:**320.