The Trials and Tribulations of Treating *Clostridium difficile* Infection—One Step Backward, One Step Forward, but Still Progress

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(See the Major Article by Johnson et al on pages 345–54.)

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Almost a decade ago, an editorial discussing the evidence concerning whether metronidazole was as efficacious as vancomycin for the treatment of *Clostridium difficile* infection (CDI) was published in the Journal. The author highlighted the need for larger, randomized prospective trials of both existing and new drugs [1]. This call has been answered, and while the primary intended outcome failed, progress has been made [2]. The report by Johnson and co-workers in this issue of *Clinical Infectious Diseases* represents another damaging blow to the case for metronidazole [2]. Ironically, the latest punch was landed in a contest between a novel toxin-binding polymer, tolevamer, and 2 old antibiotics. I say “ironically” because nonantibiotic treatment options for CDI carry a theoretically plausible advantage over agents that may add further deleterious effects to an already reeling gut microbiome; that is, staggering due to exposure to CDI-inciting antimicrobial(s). However, despite promising phase 2 results [3], tolevamer failed by a large margin in comparison with either metronidazole or vancomycin in phase 3 studies [2]. All was not lost, however, as the old antibiotic contenders threw up further compelling evidence that they are not equals [2].

Several studies, typically but not exclusively observational in design, have suggested that vancomycin is superior to metronidazole [4–7]. Unsurprisingly, if true, such superiority is most likely to be evident (and clinically relevant) in patients with severe disease [4]. This is where the story starts to get complicated. The severity of CDI has been measured using almost as many different methods as there have been treatment studies and management guidelines. For example, in the tolevamer phase 3 studies, the presence of 10 or more bowel movements/day, a peripheral white blood cell count (WBC) >20 × 10⁹/L, or severe abdominal pain was taken to indicate severe CDI [2]. Conversely, Zar et al used the presence of pseudomembranous colitis, treatment in an intensive care unit, or 2 of 4 parameters (age >60 years, temperature >38.3°C, albumin <2.5/dL, WBC >15 × 10⁹/L) [4]. To emphasize the variability here, while US (Infectious Diseases Society of America) CDI treatment guidelines use WBC (≥15 × 10⁹/L), serum creatinine (≥1.5 times the pre-morbid level), hypotension, shock, ileus, or megacolon to define severe/severe complicated CDI [8], European recommendations use a definition that is supplemented by 18 potential severity markers [9]. Thus, while these variable definitions overlap, they define different populations, which, especially for small treatment groups, may lead to different conclusions about drug efficacy. Clearly, use of the same severity definitions in all drug trials this would help with the current unwieldy process of comparing apples with pears and would help drive the design of other studies in this area. A major stumbling block is that we lack independently validated prediction tools that robustly define (therapeutic) outcomes in CDI.

A key take-home message from the tolevamer studies is that metronidazole was inferior to vancomycin in achieving clinical success (202/278, 72.7% and 210/259, 81.1%; P = .02) for all patients in the combined database [2]. Furthermore, a post-hoc multivariate analysis found that vancomycin treatment (treatment-naive status and mild or moderate CDI severity) predicted clinical success. Accepting the dangers of data overinterpretation, further clues about the relative
efficacy of vancomycin and metronidazole are evident from subgroup analyses of the combined study database. Clinical success occurred in 4%, 8.3%, and 12.2% more patients treated with vancomycin compared with metronidazole who had mild (P = .54), moderate (P = .14), and severe (P = .059) CDI, respectively. This trend toward superiority for vancomycin over metronidazole was also evident for clinical success rates in CDI due to BI strains (32/38, 84% and 34/47, 72%; P = .38) and in patients aged >65 years (110/138, 79.7% and 103/148, 69.6%; P = .072); both of these subgroups are likely to have more severe CDI. Clinical success was also (nonsignificantly) less frequent in metronidazole vs vancomycin recipients who were treated for their first recurrence of CDI (25/37, 67.6% and 25/30, 83.3%; P = .14). Thus, the dice are loaded against metronidazole as a treatment option for CDI, particularly for those with or at risk of severe infection and possibly those (with recurrence) who are more likely to have recalcitrant disease.

The poor performance of metronidazole is plausible given its pharmacokinetics compared with vancomycin [10]. Oral metronidazole is almost completely absorbed in the upper gastrointestinal tract, and modest concentrations detected in the lumen of the large intestine occur primarily via secretion across the gut mucosa. As the gut mucosa becomes less inflamed, less metronidazole crosses into the gut lumen, and thus very low concentrations of antibiotic can be found in feces later in CDI episodes [10]. By contrast, oral vancomycin 125 mg 4 times a day achieves concentrations of approximately 1000 mg/L, about 1000-fold higher than the minimum inhibitory concentration of vancomycin for C. difficile [11]. There is no good evidence that metronidazole resistance is a cause of treatment failure. However, while C. difficile strains with reduced susceptibility to metronidazole can be found, providing appropriate test methodology is used, true vancomycin resistance is exceptionally rare [12, 13].

It is plausible that the poor efficacy of tolevamer was due to suboptimal binding to toxins, which would likely be more evident in patients with severe CDI in whom toxin levels are probably higher [14]. In this context, it is pertinent that the tolevamer dosage used in the phase 3 clinical trials was higher than either of the 2 dosages studied in phase 2 [2, 3]; this was because of evidence of a dose response in phase 2 and, in turn, presumably concern that toxin binding in vivo needed to be improved. In a hamster model, 70%–90% of animals (depending on tolevamer dose) survived following C. difficile and clindamycin challenge, but a dose response was not seen in these experiments [15]. Conversely, tolevamer was ineffective in a gut model that simulated human CDI [16]. Such findings illustrate the limitations of predicting drug efficacy in CDI in preclinical testing, notably using animals that are exquisitely or variably susceptible to C. difficile challenge [17].

In line with the theory that nonantibiotics spare the gut microbiome, there was some evidence that if tolevamer effected clinical cure, treatment was less likely to be followed by recurrence of CDI [2]. However, Johnson et al rightly counsel that selection bias may be at play here, including that tolevamer responders were more likely to have mild disease. So, where does this leave the future for toxin binders? Designing (nonantibody) molecules with high affinity and avidity for C. difficile toxins but that do not bind drugs or other substrates that can be found in the gut is a tall order. Monoclonal C. difficile antitoxin antibodies are at an advanced stage in phase 3 studies and likely offer a more realistic way of neutralizing the toxins that mediate CDI [18].

A key goal is to determine whether therapeutic options have different propensities to reduce mortality associated with CDI. Recent data show an attributable mortality rate of about 8% by day 30 after diagnosis [19], although this is likely affected by C. difficile strain type and age [20, 21]. This need will grow as new, more efficacious and inevitably more costly options become available [22]. Such data are, however, unlikely to come from randomized clinical trials, especially given their tendency, for ethical and consent reasons, to recruit patients with less severe CDI. National (eg, insurance-based) databases represent a realistic way forward and could pave the way for better cost-effectiveness analyses that move us beyond arguments based solely on “cheap” vs “expensive” drugs that are based on acquisition costs alone. Metronidazole is undoubtedly inexpensive, but these new efficacy data underscore that there is much more to consider.

In an often quoted editorial written almost a decade ago, a witticism suggested that metronidazole is an option for mothers-in-law with CDI, with vancomycin preferred for mothers [23]. Remember though that all mother-in-laws are, by definition, also mothers. Does metronidazole offer a viable treatment option for CDI? Answer, yes. But the latest evidence steers us yet further away from metronidazole being the preferred option for a debilitating and costly infection [24, 25].

Note
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