Selecting Clostridium difficile Infection Outcome Measures Relevant to Public Health Concerns: Experience from a Ridinilazole Phase 2 Trial

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Abstract
Background: CDI recovers as an immediate public health threat requiring urgent and aggressive action. Recurrent CDI (rCDI) occurs in up to 39% following initial therapy and 39% following a second recurrence. Perturbation by prior antibiotics use diminishes host colitization resistance allowing C. difficile to overgrow. Current CDI therapy with vancomycin (VAN) or metronidazole causes further colitization damage to the gut microbiota (GM) primarily through GM killed and antibiotic agents are needed to tackle this CDI reinfection. Infection through (1) effectively reducing initial CDI (2) minimizing recurrence (3) and (4) preventing post-infection damage to GM. Perturbations of CDI with rCDI points to optimal selection of recipients to capture three benefits.

Methods: Randomized double-blind phase 2 study to compare 10 days RIDZ 200mg BE to VAN 500mg BE. The primary endpoint was defined as cure with no recurrence at 30 days post-end of treatment. Failures from all patients were collected at baseline, days 5, 10, 15 and 40 and at recurrence and changes to the microbiome were assessed.

Results: While clinical cure rates with RIDZ and VAN were similar, rCDI recurrent patients had a lower recurrence rate. As a result, in the primary efficacy analysis of 38 patients, 24 of 36 (66.7%) in RIDZ vs 16 of 43 (37.2%) in VAN had no recurrence (difference 29.5%, 95% CI 3.7-55.1%) without using non-responders to any salvage therapy (95% CI 0.01-59.0%). RIDZ demonstrated no significant effect in this analysis.

Sustained Clinical Response as an Outcome Measure Relevant to Public Health Concerns
- Sustained Clinical Response (SCR) is an outcome measure that is defined as clinical cure at the end of treatment period and no recurrence of CDI associated diarrhoea within the subsequent 30 days after the end of the treatment period. This accounts for differences among microbial regenerators on impact on the both the initial cure and subsequent recurrence of CDI.
- VAN is effective in providing an initial response, however, 20% to 40% of patients with resolution of initial symptoms while on VAN may have recurrence of disease, thus increasing the public health burden of C. difficile.
- Most of the previous clinical trials for evaluating treatment regimen for CDI associated diarrhoea have focused on the initial cure, or on the resolution of diarrhoea as a primary outcome measure, without taking into account the potential for disruption of the microbiome with the initial cure or the consequent potential for adverse public health impact resulting from the increased rates of recurrence.
- The profile of an antibiotic that would have the least impact on the public health burden of CDI is one that has a combination of both a high initial cure rate and a low subsequent recurrence rate. Because recurrence rates are as high after CDI, such a combination of attributes is most relevant to public health concern and is most attractive. This combination of attributes is best assessed by utilizing SCR as an outcome measure instead of cure rates.

Conclusion: CDI recurrence is a critical issue and the selection of recipients for CDI therapy is important.

Clinical Cure and Sustained Clinical Response in the Primary Analysis Population

Ridinilazole Highly Preserving of Microbiome of CDI Patients Compared to Vancomycin

Ridinilazole Statistically Superior over Vancomycin in Phase 2 Cotrily Trial

Cure at End of Treatment

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<thead>
<tr>
<th>Treatment</th>
<th>Cure at End of Treatment</th>
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<tbody>
<tr>
<td>Ridinilazole</td>
<td>77.7%</td>
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<td>Vancomycin</td>
<td>62.9%</td>
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Recurrence 30 Days Post Treatment

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<th>Treatment</th>
<th>Recurrence 30 Days Post Treatment</th>
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| Ridinilazole | 9.1%
| Vancomycin | 10.5% |

Sustained Clinical Response (SCR)

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<th>Treatment</th>
<th>Sustained Clinical Response</th>
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| Ridinilazole | 85.3%
| Vancomycin | 69.5% |

Primary analysis (HIT) population = CDI confirmed by free toxin at baseline, n = 69

Public Health Impact

Ridinilazole (200 mg) significantly improved the microbiome compared with Vancomycin (HIT). The microbiome was preserved in all patients and in patients who experienced recurrence. The microbiome was significantly more preserved in patients who achieved cure and that who achieved SCR.

Conclusions
- SCR captures the impact of a therapy on both initial cure of CDI and disease recurrence.
- Applicable in randomized studies. SCR avoids microbial changes associated with recurrence as a separate endpoint.
- By capturing impact on disease recurrence, SCR can accurately assess the suppression of novel therapy over existing agents with high cure rates.
- SCR should be a preferred measure of CDI treatment outcomes, and will be the primary endpoint in the Phase 3 trials of RIDZ 200mg BE + 200mg BE.
- These trials will also evaluate efficacy of RIDZ on gut microbiota, thereby capturing three important determinants of public health impact: Initial CDI gut microbiota, and disease recurrence.

References