Clinical Trial Design Considerations for Novel Therapies in Patients Showing Inadequate Response
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Methodological Question:

Numerous recently completed large trials with NCEs in such patients have failed to demonstrate efficacy, leading many companies to abandon schizophrenia drug development. If novel treatments are to be successfully developed, what changes in trial design, especially in selecting an appropriate treatment population, are important to increase their likelihood of success?

Background: Evidence from long-term clinical studies indicates that patients who develop treatment-resistant schizophrenia show a diminishing response to antipsychotics throughout the course of their disease. Functional imaging scans suggest that these patients have abnormal glutamate activity in the presence of normal dopamine levels. Neuroimaging and neurotransmitter findings further indicate that these changes in glutamate may precede the symptoms of schizophrenia. This contrasts with increased dopamine and normal glutamate levels observed in patients who respond to antipsychotics. These findings support the hypothesis that patients with decreased/non-response to antipsychotics that are 5-HT/D2 blockers may have improved response using glutamate modulators.

If a new chemical entity with potential to diminish effects of glutamatergic overactivity is selected for efficacy and safety evaluation in schizophrenia, multiple drug development and clinical trial design questions must be recognized and addressed for ultimate success. Among these are: selecting a readily identifiable subpopulation likely to be responsive to this intervention; choice of appropriate outcome measures; selecting the right period of observation; ensuring adherence to treatment; and managing stable baseline antipsychotic therapy that does not compromise interpretation of results of the NCE if used as an adjunctive treatment.

Methods:

A compound has been identified that blocks sodium channels leading to dose-dependent inhibition of stimulated release of glutamate release but has no effect on basal glutamate. This compound is pharmacologically specific, showing no affinity for over 130 different neurotransmitter receptors, ion channels, transporters and kinases. A double-blind, placebo-controlled, randomized, 4-week study evaluating safety, dose-titration, and preliminary evidence of efficacy of evenamide in previously responding schizophrenia patients on stable doses of risperidone or aripiprazole. 89 patients with SCZ (mean baseline PANSS total: 62.9 ± 7.4; CGI-S: 3.5 ± 0.5), were randomized (1.3:1 ratio) to treatment with evenamide (n=50) or placebo (n=39). At endpoint the addition of evenamide to risperidone or aripiprazole was associated with statistically significant efficacy, compared to placebo, based on the PANSS Positive Symptoms sub-scale [change from baseline, LS mean difference (SE): -1.28 (0.632), p=0.046; responders: 74.5% vs. 43.6%, p=0.0043), and CGI-C responders (55.3% vs. 35.9%, p=0.0855).

Two phase 3 clinical trials have been designed to demonstrate possible therapeutic effects of this agent in patients across the spectrum of treatment-resistance, from early reduced response to ultra-treatment-resistance. Selection of dose, baseline antipsychotic requirements with associated flexibility and possible biological markers will be discussed.

Conclusions:

Results are expected to provide deeper understanding of the biological underpinnings of inadequate antipsychotic-based treatment response, particularly providing evidence to the validate the hypothesis that glutamate modulation is valuable for the treatment of poorly or inadequately responsive schizophrenic patients.

Disclosures:

All authors are Newron employees and have Newron stock.