CIDP trials and tribulations

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Two publications in *JNNP* explore the potential utility of therapies with differing mechanisms of action for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Querol *et al* evaluate the neonatal Fc receptor blocker rozanolixizumab, while Doneddu *et al* study the anti-CD20 therapeutic monoclonal rituximab.[1 2] These agents, respectively, lower serum IgG levels or primarily target the preterminal B-cell lineage. In a disease where a major standard of care is a highly expensive, derived blood product with often precarious availability, which is incompletely effective, requires regular repeated infusions and does not induce long-term remission, such studies are undoubtedly welcome.

Nevertheless, both further highlight the tribulations of designing and running trials in CIDP and the intricacies of interpreting and contextualising the results. CIDP, certainly as defined by the 2010 EFNS/PNS criteria,[3] is pathogenically diverse. Current treatment regimens are highly variable. Immunological disease activity is disconnected from point measures of disability and challenging to assess. Conceptually, a response to treatment, as defined by clinical improvement, is dependent not only on suppression of disease activity but also on the variable and temporally dispersed capacity for peripheral nerves to recover. A substantial proportion of patients can be withdrawn from their existing therapies without deterioration, and both placebo and nocebo effects are prominent. In a relatively rare disease, addressing these potential problems while still evaluating sufficient patients to adequately power a trial is challenging.

Many of these issues are highlighted in the current reports. In the rozanolixizumab trial, 47% of patients in the placebo arm (and 50% in the active arm) did not relapse despite withdrawal of their existing therapy, even in the face of attempts to confirm immunoglobulin dependency prior to randomisation. Almost all patients who relapsed did so within 6 weeks, yet 24% in the placebo arm (vs none in the active arm) were previously treated with intravenous immunoglobulin at ≥6-week intervals. Clearly, many participants did not have active disease at randomisation. Furthermore, there were improvements in all three major outcome measures despite withdrawal of existing therapy, in keeping with an additional placebo response.

The open-label rituximab trial aimed to study patients not responding to conventional therapies and compared outcomes to historical controls. This study included one NF155 positive individual, who would now be considered to have a pathophysiologically distinct disorder. Lack of response was defined as a failure to improve after at least 2 weeks or 2 months of standard first-line therapy, such that a delayed response to prior therapies is a possible confound, and 5/17 continued corticosteroids during the study. Although the progressive and largely sustained improvements seen following rituximab are nevertheless encouraging, the use of historical controls, with likely differing placebo responses, makes it difficult to determine to what extent these are due to the immunological effects of the trial drug itself.

In both trials, the pharmacodynamic effects (substantial reductions in circulating IgG and CD19+ B cells, respectively) were readily apparent. A similarly objective and responsive biomarker of CIDP disease activity would help address many of the issues above but remains elusive.[4] Without this, future studies must more comprehensively exclude patients with quiescent disease, and carefully control for potential confounds, if they are to be efficient and reliable.

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