TO THE EDITOR:

Beyond NEOD001 for systemic light-chain amyloidosis

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Advances in therapy for rare diseases are causes for celebration because they are uncommon events. Conversely, decisions to close large-scale clinical trials testing promising therapies for rare diseases can cause disappointment.1 NEOD001, a monoclonal antibody (mAb) targeting light-chain amyloid (AL) fibrils tested in a phase 1/2 trial and in subsequent randomized studies, is no longer being developed by Prothena Biosciences after 1 of 3 randomized studies, PRONTO (NCT02632786), failed. The 23 April 2018 decision by Prothena to halt the other ongoing randomized trials in different AL study populations reverberated throughout the community of AL patients and physicians. As recently noted, “novel anti-amyloid treatments” that can reverse or stabilize organ impairment are an unmet need for AL patients.2 The prematurely halted randomized trials were VITAL (NCT02312206) and RAIN (NCT03168906), the former in newly diagnosed cardiac patients and the latter in treated renal patients with persistent renal impairment.

VITAL was stopped after a futility analysis was performed. The primary end point was a composite of all-cause mortality and cardiac hospitalizations as events (two-thirds of the target number of events had occurred); the hazard ratio was 0.84 favoring NEOD001 vs placebo. Because the trial was stopped, we may not learn whether NEOD001 improved overall survival in newly diagnosed AL cardiac patients, 25% of whom die within 6 months of diagnosis, although we know Prothena intends to interrogate the data with this in mind.3 The other trial, RAIN, was stopped after only 12 patients had been accrued (and 11 treated) at 3 centers; the limited data available are consistent with the renal results in the phase 1/2 studies and in the failed PRONTO trial. In the phase 1/2 trial, 60% of renal patients improved by standard criteria and in PRONTO, renal responses favored NEOD001 by 54% to 38%.4

In RAIN, patients with renal AL amyloidosis who had achieved a hematologic response to prior therapy but continued to exhibit renal dysfunction/proteinuria were randomized to receive NEOD001 24 mg/kg IV vs placebo (normal saline) every 28 days. Patients were stratified based on hematologic response and renal stage. The majority of patients had been previously treated with high-dose melphalan or bortezomib-based therapies (88% each). There were no reported infusion reactions nor were there any treatment discontinuations due to toxicity. After 23 April 2018, the RAIN study chair (R.L.C.) broke the randomization code. There were no differences in baseline proteinuria between the 6 subjects who received NEOD001 and the 5 who received placebo. NEOD001 subjects received a median of 4.5 cycles of therapy (range, 2-10) and the placebo group received 3.5 (1-6).

One patient who was receiving NEOD001 experienced an impressive renal response with 24-hour proteinuria dropping from 17 g at baseline to 4.9 g after 3 months. Responders were 2 of 6 with NEOD001 and 1 of 5 with placebo. Progression of renal disease occurred in 1 NEOD001 patient and 3 placebo patients. The paucity of these results and the imbalanced follow-up times require that we interpret these data with extreme caution; however, it is important to note that the end points of both VITAL and RAIN were not “best response” as in the phase 1/2 or PRONTO trials but rather the composite end point described above and renal response after 12 months of treatment with a confirmatory evaluation at 13 months.

NEOD001 (2A4 mAb) was developed as an antibody for secondary or amyloid A amyloidosis binding to the C-terminal region of an antigen in serum amyloid A protein bearing imperfect homology to light-chain amyloid.5 Based on limited mice data showing cross-reactivity of the antibody to AL amyloidosis, the antibody (mAb) was brought into clinical testing.6 Imaging studies showing binding in vivo to amyloid deposits were not performed as they were for CAEL-101 and GSK2315698.7,8 Should the failure of NEOD001 in 1 trial and, in our opinion, the premature termination of 2 other important randomized trials for patients with a rare disease such as AL be the end of the story? We think not. There are 3 anti-amyloid therapies actively being investigated at this time.

1. CAEL-101, formerly 11-1F4, is a chimeric mAb targeting human amyloid fibrils that has undergone extensive preclinical and in vivo testing.5,9 Its specificity for amyloid was demonstrated when 1-124–labeled 11-1F4 mAb visualized amyloid in affected organs on positron emission tomography/computed tomography imaging in human subjects.7 A phase 1 trial (NCT02245867) was completed showing that 63% of evaluable patients (5 of 8) demonstrated organ response after 1 infusion of 11-1F4 in phase 1a (and 61% of evaluable patients in phase 1b). The median time to response was 3 weeks after the start of treatment, with a tendency for faster responses at higher dosages. Organ response was independent of light-chain type10 and analysis of global longitudinal strain by echocardiogram showed significant improvement in patients with cardiac involvement.11 A randomized phase 2/3 trial for newly diagnosed patients will open in early 2019; 1 treatment arm of the phase 2 part will be a “cardiac rescue phase 2 trial” including high-risk patients with an N-terminal pro B-type natriuretic peptide > 8500 ng/L.

2. Amyloid fibrils contain the plasma protein serum amyloid P component (SAP). GSK2315698 (CPHPC) is a small molecule that depletes the circulating SAP in plasma. It is given in conjunction with an immunoglobulin G1 anti-SAP mAb that targets SAP deposits in tissues. In a phase 1 study of 15 patients with systemic amyloidosis, CPHPC and anti-SAP demonstrated the ability to clear amyloid from the liver as measured by elastography, SAP scintigraphy, and extracellular volume by magnetic resonance imaging. A reduction of the amyloid load of the kidney and lymph node were also observed.8 Currently,
this combination is being tested in an ongoing open-label nonrandomized 3-group phase 2 trial in patients with cardiac amyloidosis (NCT03044353).

3. Another interesting approach is the antibiotic doxycycline, which has been shown to interfere with amyloid fibril formation. A retrospective analysis compared 30 patients who received doxycycline in addition to standard chemotherapy to disease-matched subjects not matched for treatments. The cardiac response was 60% vs 18% and survival at 12 months 82% vs 53%.13 Two upcoming prospective studies will examine the effects of adding doxycycline to standard chemotherapy in newly diagnosed patients (NCT02207556) and to bortezomib-based therapy in newly diagnosed patients with cardiac involvement (NCT03474458).

In conclusion, the inherent challenges in clinical trial design in AL amyloidosis can impact the testing of much-needed new agents in this disease. The choices of primary and secondary end points must be carefully evaluated. Overall survival, the gold standard by which to evaluate the worthiness of an experimental agent for a lethal disease, is relevant for some and problematic for other AL study populations. Changes in biomarkers such as N-terminal pro B-type natriuretic peptide, although qualified as surrogate end points for survival in AL cardiac patients, may not always correlate with clinical disease progression as noted in trials involving immunomodulators. End points such as the 6-minute walk test and cardiac quality-of-life measures must be incorporated in future clinicals for AL as they were in VITAL and have been in transthyretin cardiac amyloidosis trials.14 The early termination of VITAL and RAIN was very disappointing and leads us to reflect on how we can improve the design of clinical trials for other promising agents such as CAEL-101, CPHPC plus anti-SAP, and doxycycline.

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