making decision, and thus continued FDG-PET/CT surveillance will be key in the management of our patient and others with MS.

FIONA HE,1 KEVIN HA,2 ZUZAN CAYCI,3 MARIA EVASOVICH SWENSON,4 M. LUÍZA CARAMORI,5 KHALID AMIN,2 MICHAEL A. L INDEN,2 AND CELALETTIN USTUN1*

1Division of Hematology-Oncology and Transplantation, Department of Medicine; 2Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota; 3Department of Radiology, University of Minnesota, Minneapolis, Minnesota; 4Department of Surgical Oncology, Minneapolis, Minnesota; 5Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, University of Minnesota, Minneapolis, Minnesota 55455, USA

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*Correspondence to: Celalettin Ustun, MD, Associate Professor of Medicine, Division of Hematology Oncology and Transplantation, Department of Medicine, University of Minnesota, 14-142 PWB, 516 Delaware Street SE, Minneapolis, MN 55455. E-mail: custun@umn.edu

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References

1. Cunningham I, Kohno B. 18 FDG-PET/CT: 21st century approach to leukemic tumors in 124 cases. Am J Hematol 2016;91:379–384.
2. Liegel J, Courville E, Sachs Z, et al. Use of sorafenib for post-transplant relapse in FLT3/ITD-positive acute myelogenous leukemia: Maturational induction and cytotoxic effect. Haematologica 2014;99:e222–e224.
3. Ansari-Lari MA, Yang CF, Tnawi-Aljundi R, et al. FLT3 mutations in myeloid sarcoma. Br J Haematol 2004;126:785–791.
4. Safarian NN, Caibere A, Bruns I, et al. Sorafenib (Nexavar) induces molecular remission and regression of extramedullary disease in a patient with FLT3-ITD+ acute myeloid leukemia. Leuk Res 2009;33:348–350.
5. Harris AC, Kitko CL, Couriel DR, et al. Extramedullary relapse of acute myeloid leukemia following allogeneic hematopoietic stem cell transplantation: Incidence, risk factors and outcomes. Haematologica 2013;98:179–184.
6. Davido MS, Kim HT, Buchreddy P, et al. Iplamumab for Patients with Relapse after Allogeneic Transplantation. N Engl J Med 2016;375:143–153.

Organ response in patients with AL amyloidosis treated with NEOD001, an amyloid-directed monoclonal antibody

To the Editor: Amyloid light chain (AL) amyloidosis is a rare disease caused by the tissue deposition of misfolded immunoglobulin light chains (LCs), produced by clonal plasma cells, that potentially cause organ dysfunction and death [1]. Plasma cell-directed (PCD) therapies inhibit abnormal LC production but do not address existing amyloid deposits. Organ responses that may accompany hematologic response (HR; reduction or complete removal of involved free LCs) are often variable and incomplete, creating a significant need for amyloid-targeted therapies to halt and potentially reverse organ dysfunction.

In preclinical studies, an anti-LC antibody, 2A4, was shown to specifically bind soluble and insoluble aggregated LCs and mediate antibody-dependent phagocytosis [2]. We have reported encouraging organ responses in a first-in-human, phase 1/2 clinical trial (NCT01707264) with NEOD001 [3], a monoclonal antibody derived from 2A4. Herein, we report detailed organ responses of two patients treated with NEOD001 after months to years of persistent organ dysfunction despite previous HR.

In preclinical studies, an anti-LC antibody, 2A4, was shown to specifically bind soluble and insoluble aggregated LCs and mediate antibody-dependent phagocytosis [2]. We have reported encouraging organ responses in a first-in-human, phase 1/2 clinical trial (NCT01707264) with NEOD001 [3], a monoclonal antibody derived from 2A4. Herein, we report detailed organ responses of two patients treated with NEOD001 after months to years of persistent organ dysfunction despite previous HR.

The phase 1/2 study design assessed NEOD001 safety and has been described [3]. Each patient had a diagnosis of AL amyloidosis and previously experienced partial or better HR to systemic therapy. Each was enrolled in a dose-escalating cohort for intravenous NEOD001 infusion every 28 days (q28d) and ultimately escalated to the maximum tolerated dose (MTD; 24 mg/kg). Each patient provided informed consent, and the trial was...
conducted in accordance with International Committee on Harmonisation Good Clinical Practice guidelines and the tenets of the Declaration of Helsinki.

In November 2009, a 60-year-old man received a diagnosis of AL amyloidosis with only renal involvement. He was previously treated with three different lines of PCD therapy. Although the patient achieved complete HR to combined bortezomib, lenalidomide, and stereoid treatment, his proteinuria persisted >3 years later.

At enrollment in January 2014, the patient’s urinary protein was 5,129 mg/day (normal, <150 mg/day). We note that persistently elevated proteinuria, especially >5,000 mg/day, will eventually lead to end-stage renal disease and necessitate dialysis [4]. This patient also had slightly elevated serum creatinine (1.4 mg/dL; normal range, 0.8–1.3 mg/dL), below normal creatinine clearance (62 mL/min; normal range, 77–160 mL/min), and an eGFR not significantly impacted at baseline.

The patient began NEO001 treatment 40.3 months after his last exposure to PCD therapy. He was treated for 9 months with 16 mg/kg NEO001 q28d, then escalated to 24 mg/kg (MTD) for the remainder of this trial. At the 5-month follow-up visit, after 4 infusions of NEO001, proteinuria was reduced by 36%, which constitutes consensus-defined renal response [4]. As of the trial cutoff date (May 9, 2016), he had received 29 infusions (20 at the MTD, Fig. 1A). His best response, recorded after 23 months of treatment, revealed an 88% reduction in proteinuria from baseline (602 mg/day). The patient’s serum creatinine levels had stabilized at 1.1 mg/dL, and his creatinine clearance had risen to fluctuate within the normal range (74–92 mL/min). The patient’s estimated glomerular filtration rate did not change from screening (52–60 mL/min/1.73 m²), indicating persistent renal dysfunction.

During the trial, the patient did not experience any serious (grade ≥3) adverse events (AEs) but did experience mild to moderate AEs possibly related to the study drug (fatigue, muscle spasms, infusion site reaction, and thrombocytopenia).

A second patient (46-year-old man) had elevated NT-proBNP levels (>3,000 pg/mL) both before he achieved CR from previous therapy (combined cyclophosphamide, bortezomib, and dexamethasone) and at screening 9.6 months later. After infusion 8 (4 mg/kg NEO001), his NT-proBNP level dropped to 219 pg/mL (~33.7% of baseline) and met consensus criteria for cardiac response [5]. At infusion 14, his dose was escalated to the MTD (orange arrow), and his best response to date was recorded after 31 infusions (~72% of baseline; 929 pg/mL NT-proBNP). The patient did experience one grade 3 SAE (chest pain), but it was deemed unrelated to NEO001, and he had not had any dose interruptions. Clinically, he experienced progressive functional improvement; edema was completely resolved, and he was no longer fatigued.

Since the study cutoff date reported here, these patients’ conditions have continued to improve. In August 2016, the renal patient’s proteinuria was 378 mg/day and the cardiac patient’s NT-proBNP level was 421 pg/mL.

Previous HR should be considered when assessing organ response after NEO001 treatment. However, organ responses in both these patients might have been specifically related to NEO001 treatment because organ improvement was not evident in the months to years after PCD treatment, suggesting that amyloid did not resolve with complete HR. Additionally, in the overall study population, neither the depth of best or last HR nor the time since best or last HR predicted response to NEO001.

These cases highlight the potential of an emerging class of AL amyloidosis drugs that directly target deposited amyloid [6], administered as combined treatment with PCD therapies or to patients who experience HR to previous systemic therapy but have persistent organ dysfunction. These cases strongly suggest that administration of NEO001 can result in organ responses not solely attributable to HR. NEO001 is being evaluated further in two randomized, placebo-controlled, global trials assessing NEO001 treatment in patients with newly diagnosed AL amyloidosis receiving standard of care (VITAL phase 3/NCT02312206) and in patients with cardiac dysfunction refractory to past systemic therapy (PRONTO phase 2b/NCT02632786).

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Authors Contribution

MAG treated patient 1. HL and BW treated patient 2. All authors wrote the manuscript and approved the final version to be submitted for publication.

MORRIS A. GERTZ,1* HEATHER J. LANDAU,2 AND BRENDAN M. WEISS3

1Division of Hematology, Mayo Clinic, Rochester, Minnesota; 2Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York; and 3Abramson Cancer Center, Division of Hematology-Oncology, University of Pennsylvania, Philadelphia, Pennsylvania

Figure 1. Renal and cardiac responses of patients after NEO001 administration. A: The urinary protein level of patient 1 (60-year-old man) was 5,129 mg/day at screening 40 months after he achieved CR from previous plasma cell-directed therapy (lenalidomide and steroid, then bortezomib and lenalidomide and steroid, then high-dose melphalan followed by autologous stem cell transplantation). After infusion 4 (16 mg/kg NEO001), reductions in his 24-hr proteinuria met renal response consensus criteria [4] (~36%; proteinuria 3,285 mg/day). The patient’s dose was escalated to the MTD at infusion 10 (orange arrow). Best renal response was measured after 23 infusions (~88% of baseline; proteinuria 602 mg/day), and he experienced no SAEs (grade ≥3) or dose interruptions. Clinically, he experienced progressive functional improvement; edema was completely resolved, and he was no longer fatigued. B: Patient 2 (46-year-old man) had elevated NT-proBNP levels (>3,000 pg/mL) both before he achieved CR from previous therapy (combined cyclophosphamide, bortezomib, and dexamethasone) and at screening 9.6 months later. After infusion 8 (4 mg/kg NEO001), his NT-proBNP level dropped to 219 pg/mL (~33.7% of baseline) and met consensus criteria for cardiac response [5]. At infusion 14, his dose was escalated to the MTD (orange arrow), and his best response to date was recorded after 31 infusions (~72% of baseline; 929 pg/mL NT-proBNP). The patient did experience one grade 3 SAE (chest pain), but it was deemed unrelated to NEO001, and he had not had any dose interruptions. Clinically, he experienced progressive functional improvement and significantly improved edema with a reduction in diuretic needs. At diagnosis, the patient had renal involvement >0.5 g/day urinary protein excretion. He achieved CR 10 months after diagnosis.

CR, complete hematologic response; MTD, maximum tolerated dose; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; SAEs, serious adverse events.

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*Correspondence to: Morie A. Gertz, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: gertz.morie@mayo.edu and sikkink.lisa@mayo.edu

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References
1. Merlini G, Comenzo RL, Seldin DC, et al. Immunoglobulin light chain amyloidosis. Exp Rev Gastroenterol Hepatol 2014;7:143–156.
2. Zago W, Renz M, Torres R, et al. NEOD001 specifically binds aggregated light chain infiltrates in multiple organs from patients with AL amyloidosis and promotes phagocytic clearance of AL aggregates in vitro. Poster presented at: 57th Annual Meeting of the American Society of Hematology; December 5–8, 2015; Orlando, Florida.
3. Gertz MA, Landau H, Comenzo RL, et al. First-in-human phase I/II study of NEOD001 in patients with light chain amyloidosis and persistent organ dysfunction. J Clin Oncol 2016;34:1097–1103.
4. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood 2014;124:2325–2332.
5. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 2012;26:2317–2325.
6. Weiss BM, Wong SW, Comenzo RL. Beyond the plasma cell: Emerging therapies for immunoglobulin light chain amyloidosis. Blood 2016;127:2275–2280.